Ladademstat in combination with paclitaxel in relapsed/refractory small cell lung carcinoma and extrapolunarily high grade neuroendocrine carcinoma

**Background:**
- Patients with extensive-stage (ES) SCLC or extra-pulmonary grade 3 NEC rapidly develop progressive disease after 1st line cytotoxic chemotherapy, and efficacious 2nd line treatment options are needed.
- Lysine Specific Demethylase 1 (LSD1, aka KDM1A) is an epigenetic enzyme that functions as a transcription co-repressor by demethylating lysine residues in histone H3 (e.g., H3K4me2) and reorganizing chromatin into a repressive conformation through specific complexes formed by LSD1 and other numerous proteins (i.e., CoREST, HDACL, and several transcription factors).
- LSD1 is overexpressed in multiple aggressive malignancies including neuroendocrine tumors and is associated with tumor progression and worse prognosis. Its inhibition reduces cancer cell growth, migration, and invasion.
- The small molecule ladamdemstat (aka ORY-1001) is a highly potent and selective oral LSD1 inhibitor (LSD1i) in Phase 2 clinical development for hematological and neuroendocrine (NE) malignancies.
- Ladademstat and other LSD1is are effective in vitro and in vivo models of SCLC by preventing the transcription factor INSM1 recruitment of LSD1 which results in NOTCH signaling activation and repression of ASCL1 with consequent reduced NE differentiation and tumor growth inhibition.
- Additionally, LSD1is have been implicated in reversing chemoresistance, synergizing with paclitaxel, and enhancing immunostimulatory responses by increasing MHC-Class I expression, IFN-Type I responses and T-cell infiltration and activity.

**Main Endpoints**
- **Primary:** Efficacy per ORR (RECIST 1.1)
- **Secondary:**
  - Safety
  - Efficacy: PFS, DoR, CBR
  - Exploratory
  - PK/PD
  - IHC (LSD1 and DNA damage)
  - Host inflammatory CTK and immune profile
  - Epigenomic and genomic/epigenetic biomarkers on tumor and PB samples

**Statistical Analysis:** Non-randomized, two cohort Phase 2 study with Simon 2-stage design.

**Current Status:** Enrolling at Fox Chase Cancer Center. Enrollment planned to begin at University of Utah and Roswell Park Cancer Center.

**Presenting author:** Next Belani, MD (Belani@fccc.edu). No conflict on interest to declare.

**Sponsor of the study:** Fox Chase Cancer Center. Funding: Oryzon Genomics SA.

---

**References:**