Introduction

• Disease background: Glioblastoma multiforme (GBM) and atypical teratoid/rhabdoid tumors (ATRT). These represent 2 extremely aggressive and lethal types of CNS malignancies sharing a median overall survival of 12-18 months and 5-year survival rate of 5 to 10% in the US [1].

• Unmet need: Blood-brain barrier (BBB) permeable agents effective against recurrent, chemotherapy-resistant central nervous system (CNS) malignancies are urgently needed.

• Proposed solution: Lantern Pharma is advancing LP-184 hydroporphyrin-methylphlorin, a tumor site activated small molecule drug candidate belonging to the acylfulvene (AF) class. LP-184 is believed to be activated via the peroxidase-catalyzed oxidation reaction by the primary peroxidase (PTGIR1). PTGIR1 expression is significantly upregulated in GBM and aorta has granted orphan drug designation (ODD) for the use of LP-184 in the treatment of both malignant glioma and ATRT, and rare pediatric disease (RPDO) for the use of LP-184 in the treatment of ATRT.

Hypothesis & Rationale

• We hypothesize that LP-184 may be a potent therapeutic as a single agent for CNS cancers expressing elevated PTGIR1.

• The rationale for this is that the activity of LP-184 is dependent upon the expression of PTGIR1. LP-184 is expected to be transformed into its bioactive form by the peroxidase activity of PTGIR1 [2].

• Belonging to the AF class of compounds, LP-184 is believed to create DNA adducts of N3 of adenine base [3] whereas Temozolomide (TMZ, the standard care agent for GBM) methylates O6 of guanine base [4]. The repair enzyme MGMT removes the primary TMZ-induced cytotoxic lesion, O6-methylguanine but not LP-184-induced DNA alkylation.

• LP-184-induced DNA damage is likely repaired preferentially via ERCC-dependent transcription couples nucleotide excision repair (TC-NER) [5].

Objectives

• Establish the therapeutic efficacy of LP-184 in GBM, ATRT and brain metastases using in vivo and in vitro models.

• Determine the effect of LP-184 + Spironolactone combination treatment on tumor cell viability.

• Determine the in vivo bioavailability of intravenously administered LP-184 in normal and tumor brain tissue.

Intravenous LP-184 induced complete and durable regression of pre-established subcutaneous U87 and M1123 GBM xenografts and prolonged survival of mice bearing orthotopic U87 and M1123 xenografts.

There is clear cooperativity between LP-184 and Spironolactone in GBM models in vivo

- Analysis of genes associated with LP-184 sensitivity in glioblastoma tumor cell lines revealed that expression of SMARCB1 is significantly anti-correlated to LP-184 sensitivity, suggesting that LP-184 will be effective in both ATRTs and other tumors with SMARCB1 loss.

- Intravenous LP-184 administration induced tumor regression in mice implanted with SMARCB1 deficient CHLA24 ATRT subcutaneous xenografts, with 2 of 10 treated mice being tumor-free after 2 cycles. Timing of doses are marked by black triangles on days 0, 2, 4, 6, 8, 14, 16, 18, 20, 22.

LP-184 CNS bioavailability and pharmacokinetics in vivo

In vivo efficacy of LP-184 in 2D models of brain metastases (day 3 treatment)

In vivo efficacy of LP-184 in 3D models of brain metastases (day 7 treatment)

Key findings and future directions

- Subcutaneous xenograft models of both GBM and ATRT showed rapid and near complete tumor regression with durable responses after 2 treatment cycles of 2 mg/kg or 4 mg/LP-184.

- Orthotopic xenograft models of GBM treated with LP-184 showed statistically significant survival benefit after a single treatment at 20 mg/kg.

- Co-treatment of several GBM cell lines with LP-184 and Spironolactone, an ERCC3 inhibitor, resulted in 3.6X increased anti-tumor activity.

- LP-184 has favorable blood brain barrier (BBB) penetration with a brain tumor plasma ratio of 0.2 (Cmax = 2539 nm).

- LP-184 BBB permeability is comparable to TMZ and brain Cmax achieved (equivalent to 800 nM) after a single i.v. infusion is greater than i.p. for sensitive GBM cell lines.

Future directions

- Phase 0/1 dose finding and toxicity studies to prepare for a phase 2 trial.