Background
Dependence of cancer cells on glutamine has made glutamine metabolism an attractive therapeutic target in cancer. Prior clinical trials evaluating glutamine analogues for the treatment of cancer were abandoned due to lack of efficacy and/or tolerability. DON (S-Di-iso-octyl-L-serine) is an irreversible inhibitor of all enzymes that utilize glutamine as a metabolic substrate. In addition to direct anti-tumor efficacy, inhibition of glutamine metabolism in the tumor microenvironment has been shown to improve T-cell activation and tumor infiltration, increasing anti-tumor immune responses. As such, DON has shown promising preclinical and early clinical activity in both preclinical and clinical settings.

The KEAP1-NRF2 pathway, an important mediator of the antioxidant capacity, in glutamine dependence in tumors. Cancers with genetic activation of the KEAP1-NRF2 subgroup of NSCLC patients who have been previously treated with a glutamine antagonist, in adult patients with advanced solid tumors

Study Design
Study Design: Multicenter, Open-Label, First-in-Human Phase 1, 2b and 2a study of DRP-104 either as a single agent or in combination with atezolizumab in adult patients with advanced solid cancers (excludes CNS and hepatocellular tumors)

PART 1: DRP-104 single-agent intravenous (IV) and subcutaneous (sQ) Dose Escalation in 8 US sites and 1 German site

An IV infusion at a mg/mL dose over 1 hour, three times a week for two weeks and on week off in 21-day cycles

A subQ injection twice a week (BRM) continuous schedule of administration (in the event of Monday/Thursday or Tuesday/Friday) defined as 21-day cycle

Cohort 1: Ph1 Safety Ph1 safety phase single agent IV and subQ in minimum 14 up to 20 adult patients/route of administration with advanced solid tumors. Once finalized and analyzed, the remaining 2 cohorts begin with the selected route of administration at the MTD/RP2D of DRP-104 for Part 2a

Cohort 2: Phase 2a single agent: 15 pts with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) with KEAP1, NFE2L2 and STK11 mutations

Cohort 3: Phase 2a single agent: up to 25 pts with recurrent, unresectable or metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

PART 3: Ph1 combination Dose Escalation of DRP-104 starting one dose below (MTD) combined with 1200mg Atezolizumab in up to 12 pts with advanced solid tumors, previously treated with an agent targeting checkpoint inhibition

PART 4: Ph1 Safety Ph1 safety Phase A combination of DRP-104 and 1200mg Atezolizumab up to 14 pts in same population as above

Study Objectives- Primary
Part 1 and Part 2 – Cohort 1: single agent dose escalation and expansion for IV and subQ in advanced solid tumors

• To characterize the safety, tolerability, dose limiting toxicities (DLTs), maximum tolerated dose (MTD)/maximum administered dose (MAD) for the IV and subQ formulations and the recommended Phase 2 dose (RP2D) and schedule for future study of DRP-104 as monotherapy (Part 2: Cohorts 2 and 3) and in combination with Atezolizumab in patients with advanced solid tumors (Parts 3 and 4) with one formulation

Part 2 – Cohort 2 (NSCLC) and Cohort 3 (SCCHN): single agent Phase 2a

• To characterize the safety and tolerability of DRP-104 as monotherapy

• To assess the overall response rate (ORR) of DRP-104 as monotherapy by response evaluation criteria in solid tumors (RECIST v1.1)

Study Objectives- Secondary
Part 1 and Part 2 – Cohort 1: single agent dose escalation and expansion for IV and subQ in advanced solid tumors

• To characterize the pharmacokinetics (PK) of DRP-104 and its metabolites as monotherapy

• To evaluate antitumor activity of DRP-104 as monotherapy in patients with advanced solid tumors

Part 2 – Cohort 2 (NSCLC) and Cohort 3 (SCCHN): single agent Phase 2a

• To characterize the PK of DRP-104 and its metabolites as monotherapy

• To evaluate duration of response (DOR), time to response (TTR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) of DRP-104 monotherapy

Parts 3 and 4: DRP-104 and atezolizumab escalation and expansion

• To evaluate the preliminary antitumor activity of DRP-104 in combination with atezolizumab

Key Eligibility
Target Population: Part 1 and Part 2 – Cohort 1: dose escalation and dose expansion in patients of advanced or recurrent, histologically or cytologically confirmed, solid malignancy that is either metastatic or unresectable

• Must have measurable disease (RECIST v1.1. Lesions)

• Must have assessed on, at least one lesion, per RECIST v1.1, decline, or be ineligible for, all available standard of care therapies

Target Population: Part 2 – Cohort 2 NSCLC:

• Locally advanced or metastatic NSCLC with known mutation in KEAP1, NFE2L2 and/or STK11 mutations (actionable mutations are included ex EGF, ALK)

• Must have received platinum containing chemotherapy & an anti-PD-(L)1 antibody unless patients declined or are ineligible for treatment

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• Must have prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition

Summary
Part 1 of the study is currently open for recruitment at 7 locations in the United States. Dose escalation continues for the IV formulation at DLS (37.5 mg/m2) and for the subQ formulation at DLS (30 mg total dose). There has been a total of 13 patients treated (7 on IV and 6 on subQ).

There have been no CTEC 2 grade 2 drug-related toxicities Pharmacokinetic data support the prodrug concept for DRP-104 is translating into the clinic.

Acknowledgement
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References

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Figure 1A. DRP-104 (sirpiglenastat) is a prodrug of the broad acting glutamine antagonist DON (S-Di-iso-octyl-L-serine). DRP-104 is inactive in its produg form with high plasma and GI tissue stability. DRP-104 is preferentially distributed in tumors where it is bio-transformed and activated to the active moiety DON.

B. Multiple glutamine dependent pathways are inhibited by DON. DON enzyme targets are indicated in bold font (4). Model of MDA of DRP-104.

Figure 2A. Anti-tumor activity of DRP-104 in patient derived KEAP1 mutant LUAD PDX models in NGS immune-compromised animals (2). Animals were dosed subcutaneously with DON (1 mg/kg) for the entire duration of two 24hr/day oral administrations. (KEAP1-KEAP1; NFE2L2-NFE2L2; STK11-STK11; KEAP1-shRNA; STK11-shRNA; NFE2L2-shRNA). KEAP1-NRF2 activity with DON treatment. Therapeutic syngeneic models mimicking tobacco induced (RT-112) (SCCHN). Treatment was 10 mg/kg anti-PD-1 in 5 or isotype control. Don was administered at 1.4 mg/kg which is the dose on day 0 for 4 cycles.