TPS3149

Trial in progress abstract: Phase 1 & phase 2a, first-in-human study (FIH) of DRP-104, a broad glutamine antagonist, in adult patients with advanced solid tumors

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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 (6-Diazo-5-oxo-L-norleucine) 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, combining DON with an immune checkpoint inhibitor (ICI), has strong rationale. The investigational product DRP-104 (sirpiglenastat) is an inactive prodrug of DON designed to limit systemic and GI tissue DON exposure while targeting glutamine dependence in tumor cells. The KEAP1-NRF2 pathway, an important mediator of the cytoprotective (antioxidant) response, is tightly regulated during normal metabolism. Cancers with genetic activation of the KEAP1-NRF2 antioxidant pathway display a metabolic imbalance supporting increased antioxidant capacity. Patients with NSCLC and genomic alterations of the KEAP1, NFE2L2 and/or STK11 have poor clinical outcomes with PD-1 inhibitors and/or chemotherapy. Consequently, this molecularly defined subgroup of NSCLC patients who have been previously treated with a platinum doublet and a PD-1 inhibitor represents a patient population with an unmet medical need and an opportunity for treatment with newer therapies such as DRP-104, a glutamine antagonist, that can lead to metabolic reprogramming of cancer cells and remodeling of the tumor immune microenvironment. Lastly, SCCHN is another tumor type where the most frequently mutated or altered genes in HNSCC have been linked to increased glutamine metabolism providing therapeutic rationale for sirpiglenastat (DRP-104) in this setting.

Mechanism of Action

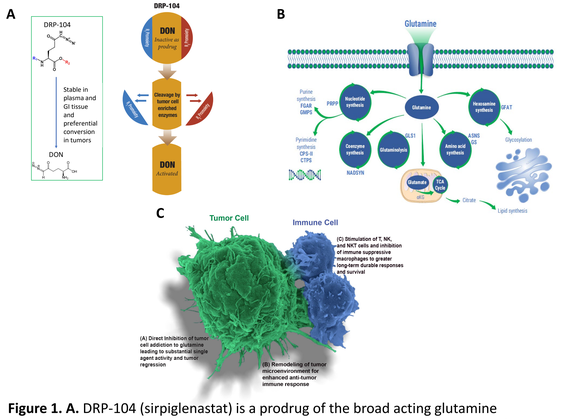

Figure 1. A. DRP-104 (sirpiglenastat) is a prodrug of the broad acting glutamine antagonist DON (6-Diazo-5-oxo-L-norleucine). DRP-104 is inactive in its prodrug form with high plasma and GI tissue stability. DRP-104 is preferentially distributed in tumors where it is bio-transformed and activated to the active moiety DON. **B.** Multiple glutamine dependent pathways are inhibited by DON. DON enzyme targets are indicated in bold font (4). **C.** Model of MOA of DRP-104.

DRP-104 Demonstrates in vivo Anti-Tumor Activity in KEAP1 Mutant NSCLC PDX and Murine SSCHN Syngeneic Models

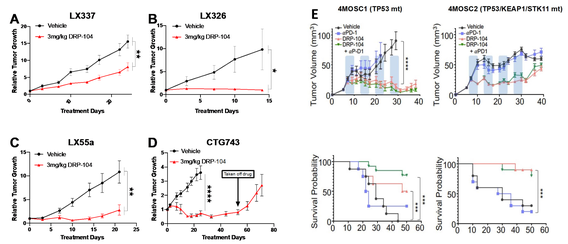

Figure 2: (A-D) Anti-tumor activity of DRP-104 in patient derived KEAP1 mutant LUAD PDX models in NSG immunocompromised animals (2). Animals were dosed subcutaneously with either vehicle or DRP-104 (3 mg/kg) daily for five days and then received a two day drug holiday. **A**)LX337: $Kras^{G12C}$; $Keap1^{G332}$ **B**) LX326: $Nras^{Q61L}$;$TP53^{R248L}$;$Keap1^{511C}$; **C**) LX55a: $Kras^{G12C}$; $TP53^{R248L}$; $Keap1^{D422N}$ **D**) CTG743: $Kras^{G12S}$;$TP53^{S215R}$; $Keap1^{H311R}$. **(E)** Anti-tumor activity with and without anti-PD-1 in two separate syngeneic models mimicking tobacco induced HPV(-) SSCHN (3). Treatment was 10 mg/kg anti-PD-1 tiw, ip or isotype control. DRP-104 was administered at 1.4 mg/kg (5 days ON/2 days OFF) for 4 cycles.

Study Design

Study Design: Multicenter, Open-label, First-in-Human Phase 1, 1b 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 (subQ) **Dose Escalation** in 8 US sites and 1 German site

An IV infusion at a mg/m^2 dose over 1 hour, three times a week for two weeks on and on week off in 21-day cycles

A subQ injection twice a week (BIW) continuous schedule of administration (e.g. Monday/Thursday or Tuesday/Friday) defined as 21-day cycle

PART 2: DRP-104 single dose **Expansion** with 3 cohorts:

- Cohort 1: **Ph1 Safety Expansion** 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 Phase2a
- Cohort 2: **Phase 2a** single agent: 55 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, un-resectable 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-1) 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 Expansion** as a combination of MTD 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 the preliminary 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 + atezolizumab escalation and expansion

- To characterize the PK of atezolizumab and DRP-104 and its metabolites
- To evaluate the preliminary antitumor activity of DRP-104 in combination with atezolizumab

Phase 2a NSCLC Expansion Subgroups Defined by KEAP1, NFE2L2 and/or STK11 mutational status (part 2/cohort 2)

Subgroup No	Main Mutation	Excluded Co-existing Mutations (referencing the original 4)*	Allowed Co-existing Mutations (referencing the original 4)**
No 1	KEAP1	STK11, NFE2L2	KRAS
No 2	STK11	KEAP1	KRAS, NFE2L2
No 3	NFE2L2	STK11	KRAS, KEAP1
No 4	KEAP1 and STK11	NFE2L2	KRAS

• Patients with known EGFR mutations, ALK rearrangements, BRAFV600E mutation, ROS1 rearrangements, NTRK gene fusion are excluded. **Other known mutations identified on the local NGS panel are allowed.
• Up to 15 pts per subgroup

Key Eligibility

Target Population: Part 1 and Part 2 – Cohort 1: dose escalation and dose expansion

- Diagnosis 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 progressed on, be intolerant of, 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 excluded i.e EGFR, ALK)
- Mutational status by locally validated DNA tests;
- Must have received platinum containing chemotherapy & an anti-PD-(L)1 antibody unless patients declined or are ineligible for treatment
- Received no more than 3 lines of anticancer therapy in the recurrent or metastatic setting

Target Population: Part 2 - Cohort 3 SCCHN:

- Recurrent, unresectable or metastatic squamous cell carcinoma of the head and neck (SCCHN) (the oropharynx, oral cavity, hypopharynx or larynx).
- Must have received platinum containing chemotherapy & an anti-PD-(L)1 antibody unless patients declined or are ineligible for treatment

Target population: Part 3 and 4 – DRP-104 + Atezolizumab dose escalation and dose expansion

- 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 DL6 (37.5 mg/m2) and for the subQ formulation at DL5 (30 mg total dose). There has been a total of 13 patients treated (7 on IV and 6 on subQ).
There have been no CTCAE ≥ Grade 2 drug-related toxicities
Pharmacokinetic data support the prodrug concept for DRP-104 is translating into the clinic.

Acknowledgement

The patients and their families who make this study possible
The clinical study teams who are participating in this study
This study is sponsored by Dracen Pharmaceuticals, Inc.
For more information visit: (NCT04471415) in clinicaltrials.gov

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