

A Phase 2 Study of DRP-104, a Glutamine Antagonist, in Patients with NFE2L2/KEAP1-altered Non-Small Cell Lung Cancer

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TRIAL IN PROGRESS

BACKGROUND

- NFE2L2/KEAP1 mutations occur in up to 30% of Non-Small Cell Lung Cancers (NSCLCs) and are associated with rapid progression, higher rates of metastatic progression, and shorter overall survival relative to wild-type NSCLCs (1-3).
- There is a significant unmet therapeutic need to target these mutations, which are associated with resistance to chemotherapy, radiotherapy, and immunotherapy (4-7).
- NFE2L2 and KEAP mutations drive metabolic reprogramming by increasing oxidative stress response pathways and enhancing dependence on glutamine, creating a therapeutic vulnerability targeted by the glutaminase inhibitor DRP-104 (8).
- DRP-104 is a novel prodrug of the glutamine antagonist 6-diazo-5-oxo-L-norleucine (DON) and is distributed systemically with preferential activation within tumor tissue, minimizing off-tumor toxicity (9) (Figure 1).
- Preclinical studies demonstrated that DRP-104 suppresses KEAP1-mutant tumor growth through direct metabolic inhibition and enhancement of anti-tumor immunity (8) (Figure 2).

Figure 1: DRP-104 mechanism of action

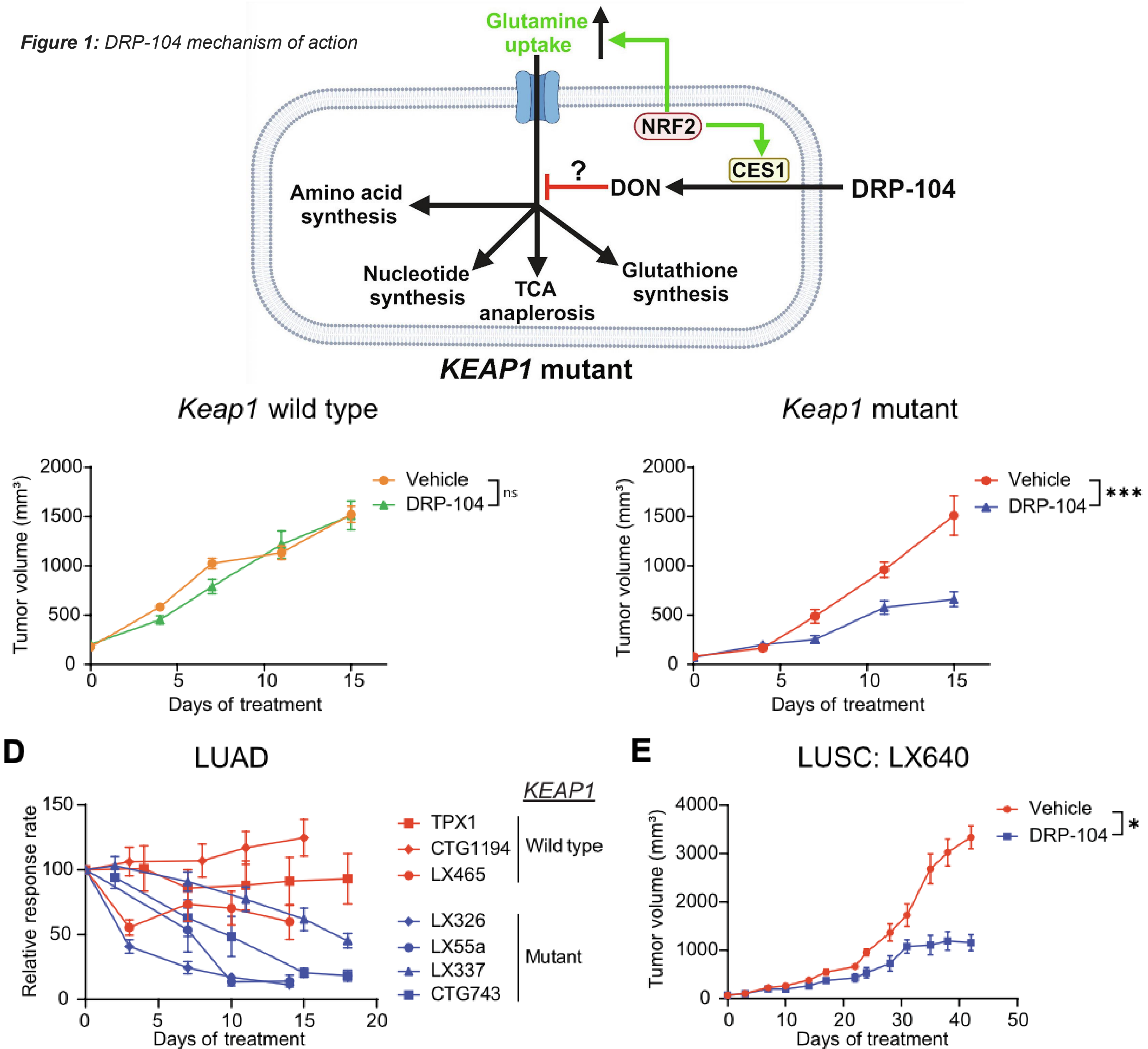


Figure 2: Preclinical evaluation in Lung Adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC) cell lines. Blue: KEAP1-mutant lung adenocarcinoma-derived xenograft lines. Red: wild-type patient-derived xenograft lines.

METHODS

STUDY DESIGN: Multicenter, Phase II, Single-arm Study

- Patients receive DRP-104 145 mg subcutaneously twice weekly on a continuous schedule in 21-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent.
- Enrollment opened on 12/1/2025, and no new safety signals have been observed to date.
- Exploratory objectives include evaluation of metabolic changes in tumors, immunologic impact on the tumor microenvironment, and the relationship between DRP-104 activity and cyclin D1 dysregulation.

Statistical Design: Simon's minimax two-stage design

- Stage 1 will enroll up to 18 patients; Stage 2 will enroll an additional 15, for a sample size of 33

Study Schema

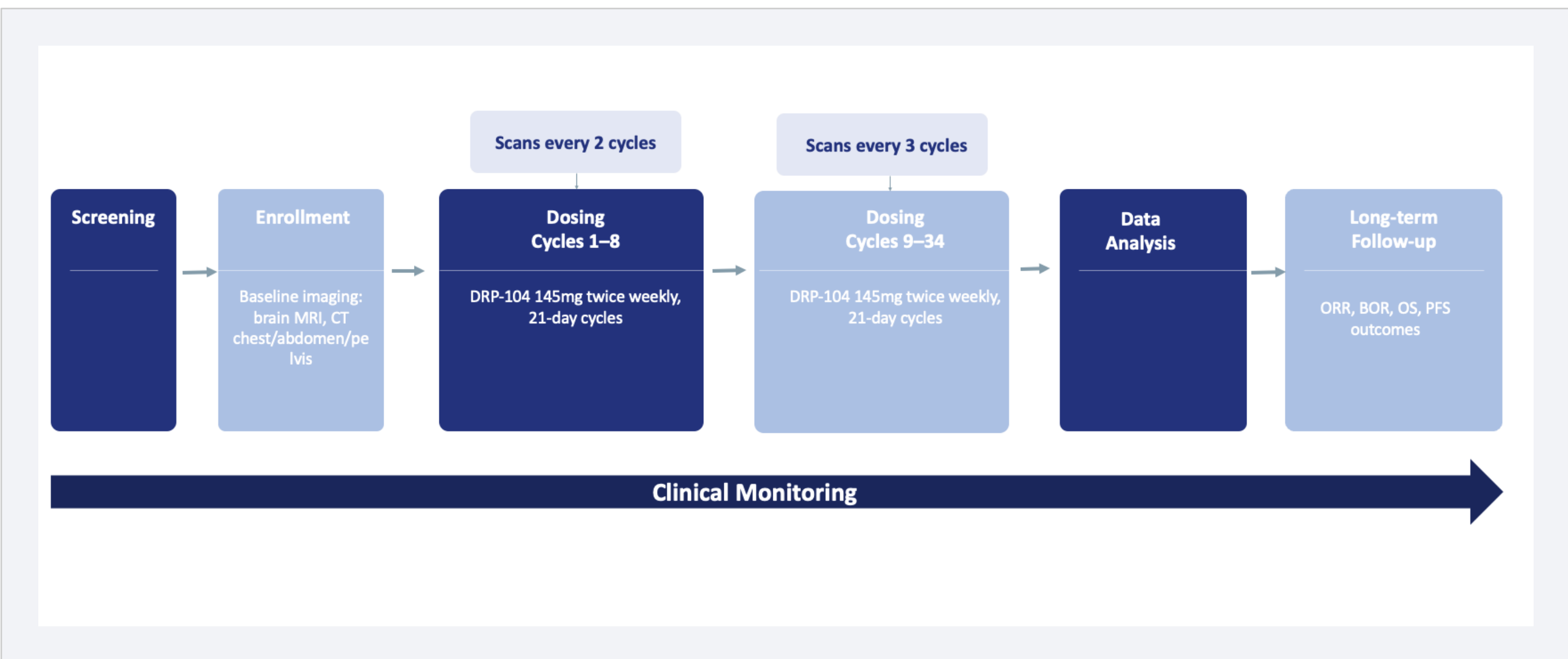


Figure 3: Study schema and treatment/assessment timeline

ELIGIBILITY CRITERIA

Age $\geq$ 18 years

Locally advanced or metastatic NSCLC

Prior treatment with chemoimmunotherapy

KEAP1 or NFE2L2 mutation present

ECOG performance status 0-1

CNS metastases eligible if treated and stable for $\geq$ 2 weeks

STUDY OBJECTIVES AND ENDPOINTS

PRIMARY OBJECTIVE

- Determine the Overall Response Rate (ORR) of DRP-104 in NFE2L2/KEAP1-mutated NSCLC.

SECONDARY OBJECTIVES

- Determine the Progression-free Survival (PFS) of patients treated with DRP-104.
- Determine the Best Overall Response (BOR) of patients treated with DRP-104.
- Determine Overall Survival (OS) of patients treated with DRP-104.
- Confirm safety profile of DRP-104.

TRIAL IN PROGRESS — CURRENTLY ENROLLING

ClinicalTrials.gov Identifier: NCT07249720

Patients are currently being enrolled at:

- NYU Langone Health, New York, NY
- Washington University in St. Louis, St. Louis, MO
- NEXT Oncology, (multiple sites)

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