Title

Phase 1 Trial of MLN0128 (Sapanisertib) and CB-839 HCl (Telaglenastat) in Patients With Advanced NSCLC (NCI 10327): Rationale and Study Design

Journal

Clinical Lung Cancer, 22(1)

ISSN

1525-7304

Authors

Riess, Jonathan W
Frankel, Paul
Shackelford, David
et al.

Publication Date

2021

DOI

10.1016/j.cllc.2020.10.006

Peer reviewed

HHS Public Access

Author manuscript

Clin Lung Cancer. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Clin Lung Cancer. 2021 January ; 22(1): 67–70. doi:10.1016/j.cllc.2020.10.006.

A Phase 1 Trial of MLN0128 (sapanisertib) and CB-839 HCl (telaglenastat) in Advanced NSCLC Patients (NCI 10327): Rationale and Study Design

Jonathan W. Riess[1], **Paul Frankel**[2], **David Shackelford**[3], **Mark Dunphy**[4], **Ramsey D. Badawi**[5,6], **Lorenzo Nardo**[5], **Simon R. Cherry**[6,5], **Ian Lanza**[4], **Joel Reid**[4], **Wilson I. Gonsalves**[4], **Charles Kunos**[7], **David R. Gandara**[1], **Primo N. Lara**[1], **Edward Newman**[8], **Paul K. Paik**[9,10]

[1]Department of Internal Medicine, Division of Hematology/Oncology. UC Davis Medical Center, UC Davis Comprehensive Cancer Center

[2]City of Hope Department of Biostatistics

[3]Department of Molecular and Medical Pharmacology, UCLA

[4]Department of Radiology, Division of Nuclear Medicine, Memorial Sloan Kettering Cancer Center

[5]Department of Radiology, Division of Nuclear Medicine, UC Davis Medical Center

[6]Department of Biomedical Engineering, UC Davis School of Medicine

[7]National Cancer Institute, Cancer Therapy Evaluation Program

[8]Department of Medical Oncology and Therapeutics Research, City of Hope

[9]Department of Medical Oncology, Memorial Sloan Kettering Cancer Center

[10]Weill Cornell Medical College

Abstract

Introduction: There are currently no approved targeted therapies for squamous cell lung cancer (LSCC) and KRAS mutant lung adenocarcinoma (LUAD). About 30% of LSCC and 25% of KRAS mutant LUAD exhibit hyperactive NRF2 pathway activation through mutations in NFE2L2 (the gene encoding NRF2) or its negative regulator KEAP1. Preclinical data demonstrate that these tumors are uniquely sensitive to dual inhibition of glycolysis and glutaminolysis via mTOR and glutaminase inhibitors. This phase 1 study was designed to assess safety and preliminary activity of the mTOR inhibitor sapanisertib (MLN0128) in combination with the glutaminase inhibitor, CB-839.

Corresponding Author: Jonathan W. Riess, MD MS, Associate Professor, Department of Internal Medicine, Division of Hematology/Oncology, UC Davis Comprehensive Cancer Center, Sacramento, CA/United States of America, jwriess@ucdavis.edu.

Methods—Phase 1 dose finding will use the queue-based variation of the 3+3 dose escalation scheme with the primary endpoint of identifying the recommended expansion dose. Subsequently, patients will enroll into four expansion cohorts (N=14 per cohort): 1) LSCC harboring *NFE2L2* or 2) *KEAP1* mutations or 3) LUAD harboring *KRAS*/(*KEAP1* or *NFE2L2*) co-alterations, or 4) LSCC WT for *NFE2L2* and *KEAP1* to confirm acceptable tolerability of the RED. The primary endpoint of the dose expansion is to determine the preliminary efficacy of MLN0128/CB-839 combination therapy.

Conclusion—This phase 1 study will determine the RED and preliminary efficacy of sapanisertib (MLN0128) and CB-839 in advanced NSCLC with a focus on subsets of LSCC and KRAS mutant LUAD harboring NFE2L2 or KEAP1 mutations.

Microabstract

About 30% of LSCC and 25% of KRAS mutant LUAD exhibit hyperactive NRF2 pathway activation through mutations in NFE2L2 or its negative regulator KEAP1. Preclinical data demonstrates these tumors are uniquely sensitive to dual inhibition of glycolysis and glutaminolysis via mTOR and glutaminase inhibitors, respectively. This phase 1 study was designed to assess safety and preliminary activity of the mTOR inhibitor sapanisertib in combination with the glutaminase inhibitor CB-839.

Keywords

Squamous cell lung cancer; Lung adenocarcinoma; Glycolysis; Glutaminolysis; NRF2; KEAP1

Introduction:

Patients with stage IV squamous cell lung cancer (LSCC) account for 25% of all NSCLC diagnosed worldwide, amounting to 40,000 new cases annually in the United States and 350,000 annually worldwide(1). While oncogene driven lung cancers have seen 7 therapies approved that target alterations that typically occur in lung adenocarcinomas, patients with LSCC have seen little advancement in targeted therapies(2).

The NRF2 pathway (encoded by *NFE2L2*) is a transcription factor that activates antioxidant response elements and is frequently hyperactive in NSCLC. *NFE2L2* mutations disrupt KEAP1 binding and upregulate mTOR through RagD(3). KEAP1 is a tumor suppressor that negatively regulates NRF2 and sequestering NRF2 to the cytoplasm. *NFE2L2* and *KEAP1* mutations occur in approximately 30% of LSCCs and 25% of *KRAS* mutant NSCLCs(4–6). Patients with lung cancers containing *NFE2L2* and *KEAP1* co-mutations lack effective treatments, and new therapeutic approaches are needed to improve outcomes for these patients.

In an NCI sponsored phase 2 trial of the mTOR inhibitor MLN0128 (sapanisertib) in *NFE2L2* or *KEAP1*-mutant stage IV LSCC and *KRAS* mutant lung adenocarcinoma (LUAD) preliminary activity was noted in evaluable NFE2L2 mutant LSCC(7). CB-839 HCl (telaglenastat) is a first in class oral glutaminase inhibitor that blocks tumor glutamine consumption. Glutaminase inhibitors have synergistic anti-tumor efficacy with MLN0128 (sapanisertib) in NRF2 upregulated NSCLC(8). Glutaminase is a mitochondrial enzyme that

is the rate limiting step for conversion of glutamine to glutamate. Tumor cells consume glutamine for biosynthesis, proliferation and regulation of oxidative stress. When glycolysis is inhibited by mTOR inhibition with MLN0128, the GSK3 signaling axis circumvents mTOR inhibition of glycolysis in LSCC, leading to increased glutaminase expression and a metabolic switch to glutamine to fuel the Krebs cycle(9). This adaptive glutaminolytic switch is potentially actionable via dual inhibition of glycolysis with MLN0128 (sapanisertib) and glutaminolysis with CB-839.

NRF2 pathway aberrant LUAD may also be particularly sensitive to dual mTOR and glutaminase inhibition. For example, *KEAP1* loss in a *KRAS*-driven lung cancer model leads to hyperactive NRF2 signaling and resistance to multiple oxidative stress agents with these tumors preferentially sensitive to glutaminase inhibition with CB-839(10). *KRAS* mutant *STK11* and *KEAP1/NFE2L2* mutant lung cancers exhibited enhanced glutamine dependence with *in vivo* inhibition of tumor growth when treated with CB-839 compared to *KRAS* models without *STK11* or *KEAP1* co-mutations(11). This phase 1 study was initiated to determine the safety, tolerability and preliminary efficacy of sapanisertib and CB-839 in NSCLC with a focus on NRF2 hyperactive subsets of LSCC and *KRAS* mutant LUAD harboring *KEAP1* or *NFE2L2* mutations.

Methods:

Study Design

This is a phase 1/1b trial open to patients with any NSCLC during the dose finding phase, with expansion cohorts at the recommended phase 2 dose (RP2D) for patients with LSCC and an additional molecularly selected NSCLC: LSCC harboring 1) *NFE2L2* or 2) *KEAP1* mutations or 3) LUAD harboring *KRAS*/(*KEAP1* or *NFE2L2*) co-alterations, or 4) LSCC WT for *NFE2L2* and *KEAP1* (Figure 1). The expansion cohort will help confirm the acceptable toxicity/tolerability of the recommended expansion dose (RED) and provide a preliminary assessment of the efficacy of the combination in selected LSCC and *KRAS* mutant NSCLC patient populations. Acceptable molecular testing platforms include: Foundation CDx, Foundation ACT, Guardant 360 and MSK-IMPACT. Plasma circulating tumor (ct)DNA performed by Foundation ACT or Guardant 360 will only be accepted if a positive test.

The dose escalation portion will use the queue-based variation of the 3+3 dose escalation scheme (IQ 3+3) which restricts patients' risk to the limits found in the traditional 3+3 design while allowing for additional accruals to reduce study duration

All toxicities will be graded using NCI CTCAE Version 5.0. The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the investigator to be possibly, probably or definitely related to study drug administration:

- ≥ Grade 3 clinically significant non-hematological toxicity despite adequate treatment, excluding:

  Reversible grade 2 nausea/vomiting/diarrhea, or readily reversible grade 3 metabolic/electrolyte lab values

- Grade 3 hyperglycemia lasting ≤14 days (all patients should receive optimal antiglycemic treatment, including insulin, as clinically indicated)
- Grade 3 rash lasting ≤3 days (all patients should receive topical steroid treatment, oral antihistamines, and oral steroids, if necessary).
- Inadequately treated grade 3 nausea and/or vomiting and grade 3 diarrhea (all patients should receive optimal antiemetic and/or antidiarrheal prophylaxis and/or treatment).
- Febrile neutropenia; grade 4 anemia; thrombocytopenia, or thrombocytopenic bleeding
- Delay in starting cycle 2 of ≥14 days due to toxicity related to one or more protocol drugs
- Dose intensity in cycles beyond cycle 1 will be considered in the assessment of the RP2D
- To be evaluable for a DLT, 80% of doses must have been administered in cycle 1 unless a DLT occurred.

Key Eligibility Criteria

- Dose escalation - patients must have Stage IV or recurrent/metastatic NSCLC and have progressed on or after platinum-based chemotherapy and/or PD-(L)1 immune checkpoint inhibitor.
- Dose expansion - patients must have Stage IV or recurrent/metastatic NSCLC harboring 1) *NFE2L2* mutations (LSCC); 2) *KEAP1* mutations (LSCC); *KRAS/KEAP1* or *KRAS/NFE2L2* co-mutations (non-squamous NSCLC); or 3) LSCC WT for *NFE2L2* or *KEAP1* who have progressed on or after platinum-based chemotherapy and/or PD-(L)1 immune checkpoint inhibitors or immunotherapy.
- ECOG performance status 0–2
- Measurable disease by RECIST 1.1.
- Adequate organ function
- Fasting blood glucose (FBS) ≤130 and HGBA1C ≤ 8.0% and fasting triglycerides ≤ 300 mg/dL.

Study Endpoints

Imaging assessment will be performed every 2 cycles (about every 8 weeks) with response assessment by RECIST 1.1.

The primary endpoint in dose escalation is to determine the maximum tolerated dose//RP2D of MLN0128 (sapanisertib) and CB-839 HCl (telaglenastat) in combination against advanced NSCLC.

The primary endpoints in dose expansion are to determine the preliminary efficacy of MLN0128 (sapanisertib) and CB-839 HCl (telaglenastat) in select genotypic and histologic

cohorts of advanced NSCLC (*NFE2L2* LSCC; *KEAP1* LSCC; NSCLC *KRAS/KEAP1* or, *KRAS/NFE2L2* non-squamous NSCLC and LSCC negative for *NFE2L2* or *KEAP1* mutations).

Study Assessments

Associated correlative studies include broad genomic profiling by tissue and plasma. Plasma amino acid metabolite and pharmacokinetic profiling, intratumoral metabolic signaling profiling by IHC and RPPA and paired ^{18}F-Glutamine positron emission tomography (PET) (^{18}F-Gln) and ^{18}FDG-PET analyses at MSKCCC and UC Davis to image glucose and glutamine metabolism in response to dual inhibition of glycolysis and glutaminolysis with sapanisertib and CB-839, respectively. ^{18}F-FDG is a glucose analog that enters the cell where it is phosphorylated become ^{18}F-FDG-6 phosphate. After a reasonable uptake period, ^{18}F concentration as measured by PET then becomes a semi-quantitative marker of glucose metabolism(12) (12). ^{18}F-Gln enters the cell via ASCT2 and other transporters where it may be converted to ^{18}F-fluoroglutamate, a process which is catalyzed by glutaminase and which is the rate-limiting step for glutaminolysis. ^{18}F-Gln uptake has been shown to be enhanced in glutamine-avid tumors (13). Total-body dynamic PET imaging (14), will enable fully quantitative analysis of glucose utilization (for ^{18}F-FDG) and glutamine transport and conversion to glutamate (for ^{18}F-Gln) for all lesions.

Statistical Analysis

Response rate will be calculated for each cohort along with an exact 95% confidence interval. With 14 patients in each genotype cohort, if the true response is 20%, there is less than a 5% chance that no responders would be observed, and the response can be estimated with a standard error of 13% or less.

Discussion

Lung cancers characterized by hyperactivation of NRF2 and consequently, glycolysis currently lack effective treatment options. To date, there are no approved targeted therapies for LSCC and *KRAS*-mutant LUAD. NRF2 hyperactive subsets of LSCC and *KRAS*-mutant LUAD represent a substantial subset of these lung cancers (25–30%). This phase 1/1b trial will determine the recommended expansion dose of a promising new treatment option utilizing an mTOR inhibitor, MLN0128 in combination with the glutaminase inhibitor, CB-839. Expansion cohorts at the RP2D for patients with LSCC and additional molecularly selected lung cancers will examine preliminary clinical activity in these select histologic and molecular subsets that we anticipate will preferentially benefit from dual inhibition of glycolysis and glutaminolysis. Broad genomic profiling using tissue and plasma, plasma amino acid metabolite and pharmacokinetic profiling, and intratumoral metabolic profiling will interrogate additional factors beyond *NFE2L2* and *KEAP1* mutations that may underlie clinical activity of the combination. ^{18}F-GLN and ^{18}FDG-PET analyses will non-invasively explore changes in glucose and glutamine metabolism in response to dual inhibition of glycolysis and glutaminolysis.

Conclusion

This study will determine the RP2D of MLN0128 and CB-839 combination therapy. Expansion cohorts will examine preliminary efficacy in LSCC in NRF2 hyperactive lung cancers with either *NFE2L2* or *KEAP1* mutations or in *KRAS*-mutant LUAD and LSCC. A LSCC cohort WT for *NFE2L2* and *KEAP1* mutations will also be assessed to examine preliminary efficacy in these hypermetabolic tumors, as additional preclinical data suggest that targeting glucose and glutamine metabolism with MLN0128 and CB-839 might be operant in other LSCC context identifiable through assessment of the GSK3 and GLS pathways(9). If preliminary activity is established at the RP2D, we plan future larger studies focused on NRF2 pathway aberrant molecular and histologic subsets that may underlie preferential activity of the combination.

Acknowledgements:

This trial is sponsored by the National Cancer Institute Cancer Therapy Evaluation Program (NCI-CTEP) under grant UM1-CA186717.

Disclosures

Jonathan Riess reports personal fees from Blueprint, personal fees and non-financial support from Novartis, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Celgene, non-financial support from AstraZeneca, personal fees and non-financial support from Spectrum, personal fees from Loxo Oncology, personal fees from Genentech, personal fees from Medtronic, non-financial support from Merck, non-financial support from Revolution Medicines, outside the submitted work. Paul Paik reports personal fees from Boehringer Ingelheim, personal fees from Takeda, personal fees from Celgene, personal fees from EMD Serono, personal fees from Calithera, personal fees from AstraZeneca, personal fees from Abbvie, personal fees from Lilly Oncology, outside the submitted work.

David Gandara reports grants from Amgen, other from AstraZeneca, other from Guardant, from Oncocyte, from IO Biotech, from Ocean Genomics, personal fees and other from Roche-Genentech, outside the submitted work. Lorenzo Nardo has is principle investigator of a service agreement with United Imaging Healthcare.

References:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30. [PubMed: 31912902]
2. Calles A, Riess JW, Brahmer JR. Checkpoint Blockade in Lung Cancer With Driver Mutation: Choose the Road Wisely. Am Soc Clin Oncol Educ Book. 2020;40:372–84. [PubMed: 32421452]
3. Shibata T, Saito S, Kokubu A, Suzuki T, Yamamoto M, Hirohashi S. Global downstream pathway analysis reveals a dependence of oncogenic NF-E2-related factor 2 mutation on the mTOR growth signaling pathway. Cancer Res. 2010;70(22):9095–105. [PubMed: 21062981]
4. Cancer Genome Atlas Research N. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012;489(7417):519–25. [PubMed: 22960745]
5. Paik PK, Shen R, Won H, Rekhtman N, Wang L, Sima CS, et al. Next-Generation Sequencing of Stage IV Squamous Cell Lung Cancers Reveals an Association of PI3K Aberrations and Evidence of Clonal Heterogeneity in Patients with Brain Metastases. Cancer Discov. 2015;5(6):610–21. [PubMed: 25929848]
6. Arbour KC, Jordan E, Kim HR, Dienstag J, Yu HA, Sanchez-Vega F, et al. Effects of Co-occurring Genomic Alterations on Outcomes in Patients with KRAS-Mutant Non-Small Cell Lung Cancer. Clin Cancer Res. 2018;24(2):334–40. [PubMed: 29089357]
7. Paik PK, Ahn L, Ginsberg MS, Plodkowski AJ, Kim R, Doyle LA, et al. Targeting NFE2L2/KEAP1 mutations in advanced NSCLC with the TORC1/2 inhibitor TAK-228. J Clin Oncol. 2019;37.
8. Paik PK, Riess JW. Sapanisertib and CB-839. IASLC Targeted Therapies. 2020;2.

9. Momcilovic M, Bailey ST, Lee JT, Fishbein MC, Braas D, Go J, et al. The GSK3 Signaling Axis Regulates Adaptive Glutamine Metabolism in Lung Squamous Cell Carcinoma. Cancer Cell. 2018;33(5):905–21 e5. [PubMed: 29763624]

10. Romero R, Sayin VI, Davidson SM, Bauer MR, Singh SX, LeBoeuf SE, et al. Keap1 loss promotes Kras-driven lung cancer and results in dependence on glutaminolysis. Nat Med. 2017;23(11):1362–8. [PubMed: 28967920]

11. Galan-Cobo A, Sitthideatphaiboon P, Qu X, Poteete A, Pisegna MA, Tong P, et al. LKB1 and KEAP1/NRF2 Pathways Cooperatively Promote Metabolic Reprogramming with Enhanced Glutamine Dependence in KRAS-Mutant Lung Adenocarcinoma. Cancer Res. 2019;79(13):3251–67. [PubMed: 31040157]

12. Gillies RJ, Robey I, Gatenby RA. Causes and consequences of increased glucose metabolism of cancers. J Nucl Med. 2008;49 Suppl 2:24S–42S. [PubMed: 18523064]

13. Grkovski M, Goel R, Krebs S, Staton KD, Harding JJ, Mellinghoff IK, et al. Pharmacokinetic Assessment of 18F-(2S,4R)-4-Fluoroglutamine in Patients with Cancer. J Nucl Med. 2020;61(3):357–66. [PubMed: 31601700]

14. Zhang X, Xie Z, Berg E, Judenhofer MS, Liu W, Xu T, et al. Total-Body Dynamic Reconstruction and Parametric Imaging on the uEXPLORER. J Nucl Med. 2020;61(2):285–91. [PubMed: 31302637]

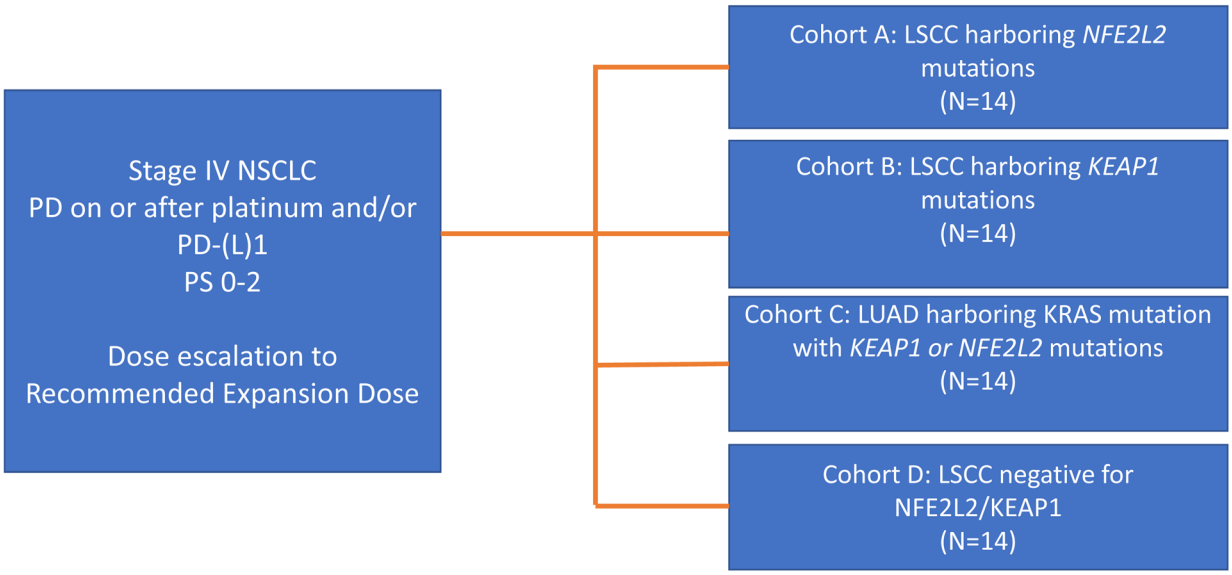

Figure 1:
Trial Schema of A Phase 1 Trial of MLN0128 (sapanisertib) and CB-839 HCl (telaglenastat) in Advanced NSCLC Patients (NCI 10327)