INTRODUCTION

- For patients with non-small cell lung cancer (NSCLC), effective second-line treatment options are limited.
- Pembrolizumab (pembro), a PD-1–blocking antibody, is indicated in patients with metastatic NSCLC whose tumors express PD-L1 and who have disease progression on or after platinum-based chemotherapy.
- CC-486, an oral formulation of azacitidine, has shown promising activity as a priming agent for chemotherapy in patients with relapsed/refractory solid tumors.
- CC-486 may modulate immunoregulatory pathways and sensitize tumor cells to treatment with checkpoint inhibitors.
- The combination of CC-486 and pembro is being investigated in this study as a second-line treatment for patients with locally advanced/metastatic NSCLC.

OBJECTIVE

- To evaluate the efficacy and safety of CC-486 + pembro vs pembro + placebo in second-line treatment of patients with locally advanced/metastatic NSCLC.

METHODS

Endpoints

Primary
- PFS, defined as time from randomization to investigator-assessed disease progression based on RECIST v1.1 or death by any cause, whichever occurs earlier.
- ORR (CR + PR) by RECIST v1.1.
- OS.
- Safety.
- Pharmacokinetics.

Secondary
- Disease control rate (DCR) ≥ 18
- ORR (CR + PR) by RECIST v1.1.
- OS.
- Safety.
- Pharmacokinetics.

Exploratory
- Immune-related efficacy (irPFS, irORR, irDCR).
- Tumor PD-L1 expression.
- Tumor-infiltrating lymphocytes.
- Gene expression and DNA methylation analyses of tumors and/or blood.

Key Inclusion Criteria

- Age ≥ 18 years.
- Histologically and/or cytologically confirmed squamous or nonsquamous NSCLC, with only 1 prior systemic platinum therapy.
- Stage IIIb or IV NSCLC with measurable disease per RECIST v1.1.
- ECOG PS 0 – 1.
- Adequate organ and bone marrow function.
- - AST and ALT ≤ 2.5 × ULN or ≤ 5.0 × ULN if liver metastasis present.
- - Total bilirubin ≤ 1.5 × ULN and serum creatinine ≤ 1.5 × ULN.
- - ANC ≥ 1.5 × 10⁹ cells/L, platelets ≥ 100 × 10⁹ cells/L, Hb ≥ 9 g/dL.

Key Exclusion Criteria

- > 1 prior line of therapy for stage IIIb or IV disease.
- Nonsquamous histology with known or unknown sensitizing EGFR and/or positive ALK mutation.
- Previously treated with azacitidine, decitabine, or any other hypomethylating agent.
- Prior therapy with any other anti-PD-1, -PD-L1 or -PD-L2 agent or antibody targeting other immunoregulatory receptors or mechanisms, including treatment with pembrolizumab.
- History of interstitial lung disease or pneumonitis that has required oral or IV steroids.
- Uncontrolled or symptomatic central nervous system metastases.
- History of IBD, celiac disease, or other GI disorders, including persistent diarrhea.
- Known history or current diagnosis of HBV, HCV, tuberculosis or HIV.

Key Exclusion Criteria

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- Age ≥ 18 years.
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- Stage IIIb or IV NSCLC with measurable disease per RECIST v1.1.
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STUDY DESIGN

NCT02546986

CC-486 300 mg QD on days 1-14 + pembrolizumab 200 mg on day 1 of a 21-day cycle

Placebo QD on days 1-14 + pembrolizumab 200 mg on day 1 of a 21-day cycle

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DOSE MODIFICATIONS

- Upon dose reduction, patient can not return to original dose of CC-486.
- Dose of CC-486 can be reduced from 300 mg to 200 mg.
- If > 1 reduction, CC-486 will be discontinued.
- Patient will be followed for efficacy and safety of pembrolizumab alone.
- CC-486 may be withheld for ≤ 7 days between cycles to allow hematologic criteria to recover and for ≤ 14 days due to unacceptable toxicity.
- Dose reduction is required after 7 days of dose interruption.
- Dose reductions are not permitted for pembrolizumab.
- Pembrolizumab must be discontinued for severe drug-related toxicities and severe or life-threatening AEs listed below.

STATISTICAL ANALYSIS

- Nine patients were randomized 1:1 to receive CC-486 + pembrolizumab or pembrolizumab + placebo. Primary analysis will be conducted when 70 PFS events occur.
- PFS and OS summarized by median time to event, including 2-sided 90% CI, for each treatment group and within each strata.
- Hazard ratio and two-sided 90% CI for PFS and OS will be estimated using Cox proportional hazards model with treatment and any stratification factors as model covariates.
- Investigator-assessed ORR and DCR will be determined using RECIST v1.1.
- irPFS, irORR, and irDCR will be analyzed using the same statistical methods previously described for similar endpoints, if sufficient data are collected.
- 100 patients are currently enrolled.

CONCLUSIONS

- This phase II study will evaluate the efficacy and safety of CC-486 + pembrolizumab vs pembrolizumab + placebo in the second-line treatment of patients with locally advanced/metastatic NSCLC.
- Identification of serum and tissue biomarkers will be undertaken to better characterize patients more likely to respond to this combination.
- This is the first study to evaluate CC-486, an immune sensitizing agent, in combination with a checkpoint inhibitor in patients with advanced NSCLC.
- The results from this study may help determine whether CC-486 in combination with pembrolizumab is an effective second-line treatment option in patients with advanced NSCLC.

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DISCLOSURES

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REFERENCES
