ALLIANCE FOUNDATION TRIALS, LLC

AFT-07 (M14-360): A Phase 1 Dose Escalation and Phase 2 Randomized, Placebo-Controlled Study of the Efficacy and Tolerability of Veliparib in Combination with Paclitaxel/Carboplatin-Based Chemoradiotherapy Followed by Veliparib and Paclitaxel/Carboplatin Consolidation in Subjects with Stage III Non-Small Cell Lung Cancer (NSCLC)

Joseph K. Salama, MD, Duke University Medical Center
Thomas Stinchcombe, MD, Duke University Medical Center

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RATIONALE

- Chemoradiotherapy is the standard therapy for unresectable stage IIIA and IIIB NSCLC.
- Current standard therapy for stage III NSCLC provides a progression-free survival (PFS) of approximately 12 months, and a median overall survival of approximately 24-28 months.
- Phase 2 data of the PARP inhibitor veliparib with paclitaxel and carboplatin in metastatic NSCLC suggests the addition of veliparib may improve outcomes of patients with advanced NSCLC.
- Veliparib may also increase the efficacy of platinum-based therapy and radiation therapy.
- This study will investigate concurrent radiotherapy and consolidation chemotherapy with veliparib for stage III NSCLC.

OBJECTIVE

Primary

- **Phase 1:** To establish the recommended Phase 2 dose (RPTD) of veliparib in combination with concurrent paclitaxel/carboplatin-based chemoradiotherapy
- **Phase 2:** To investigate veliparib concurrent with thoracic radiation and versus placebo, and with consolidation carboplatin and paclitaxel with veliparib compared to placebo

Primary for Phase 2:

- Progression-free survival (PFS) in patients with stage III non-small cell lung cancer (Phase 2 portion)

Secondary for Phase 2

- To assess overall survival (OS), objective response rate (ORR)
- To assess the duration of overall response (DOR)
- To assess the safety and tolerability of veliparib versus placebo added to standard therapy

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Overall Design and Plan

This two-phase study consists of:

- Dose-escalation of veliparib to determine an RPTD for combination with concurrent paclitaxel/carboplatin-based CRT.
- A randomized, double-blinded study to determine whether veliparib improves outcome relative to placebo when added to paclitaxel/carboplatin based CRT followed by consolidation paclitaxel/carboplatin in subjects with previously untreated stage III NSCLC.

Selection of Study Population

- The study was designed to enroll approximately 174 subjects with stage III NSCLC (approximately 18 in the dose escalation portion)
- Approximately 156 (in the randomized portion) at approximately 50-75 study centers

Dose Escalation Portion (Phase 1) Subjects will receive veliparib in combination with carboplatin AUC 2 + paclitaxel 45 mg/m2 + thoracic radiotherapy to a total dose of 60-63 Gy. Dose escalation of veliparib during chemoradiotherapy will occur in cohorts derived from the 3+3 design. The study is currently on hold after enrolling the 240 mg twice daily cohort, and a 240 mg twice daily with consolidation carboplatin/paclitaxel cohort.

Randomized (Phase 2 Portion) Following the dose escalation portion of the study, the RPTD will be determined. The sponsor and the study will review Phase 2 study design. The current design will begin with patient randomization in a 1:1:1 ratio to the treatment arms as follows:

(A) Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/veliparib

(B) Concurrent paclitaxel/carboplatin/radiotherapy/veliparib followed by consolidation paclitaxel/carboplatin/placebo

(C) Concurrent paclitaxel/carboplatin/radiotherapy/placebo followed by consolidation paclitaxel/carboplatin/placebo

STUDY SCHEMA

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Concurrent Chemoradiotherapy

- Veliparib will be administered PO BID beginning 3 days prior to beginning chemoradiotherapy. Chemotherapy will consist of carboplatin AUC 2 mg/mL/min and paclitaxel 45 mg/m2 administered intravenously on Day 1 of each week during radiotherapy. Radiotherapy will be delivered using 3D conformal RT or IMRT and subjects will receive a total of 60-63 Gy. Chemoradiotherapy may be extended up to 9 weeks in duration due to treatment delays. Subjects who have not completed chemoradiotherapy after 9 weeks should proceed to consolidation therapy or observation at the discretion of the Investigator.

Consolidation Chemotherapy

- No more than 8 weeks after completion of concurrent chemoradiotherapy, veliparib/placebo 120 mg BID will be administered beginning 2 days prior to the start of paclitaxel/carboplatin infusion and will continue through Day 5 of each 21-day cycle.
- Carboplatin AUC 6 mg/mL/min and paclitaxel 200 mg/m2 will be administered intravenously on Day 1 of each 21-day cycle. Subjects will receive a maximum of 2 cycles of consolidation chemotherapy. Subjects who require > 8 weeks to recover from toxicities resulting from chemoradiotherapy should not receive consolidation.
- Amendment 4 tested an increased consolidation veliparib dose of 240 mg PO BID with carboplatin and paclitaxel.

TREATMENT PLAN / INTERVENTION

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- Subject must be ≥ 18 years of age.
- Subject must have histologically or cytologically confirmed stage III NSCLC.
- When pleural fluid is visible on the CT scan or on a chest x-ray, a thoracentesis is required to confirm that the pleural fluid is serous **and** cytologically negative. Effusions that are minimal (i.e., not visible on chest x-ray) or that are too small to safely tap are exempted from the requirement for thoracentesis.
- Subjects in the randomized portion of the study must have measurable disease per RECIST version 1.1 criteria.
- Subjects must have V20 (volume of lung to receive 20 Gy or more radiotherapy according to simulation) < 35%.
- Eastern Cooperative Oncology Group (ECOG) performance score of 0-1.

KEY ELIGIBILITY CRITERIA

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CONTACT US

Study Chairs
Joseph K. Salama, MD
Duke University Medical Center
E-mail: joseph.salama@duke.edu

Thomas Stinchcomb, MD
Duke University Medical Center
E-mail: thomas.stinchcombe@duke.edu