

SWOG S0802: A Randomized Phase II Trial of Weekly Topotecan with and without AVE0005 (Aflibercept; NSC-724770) in Patients with Platinum Treated Extensive Stage Small Cell Lung Cancer (E-SCLC)

Fast Facts

AVE005 provided.

ELIGIBILITY CRITERIA

1. Patients must have a histologically or cytologically confirmed diagnosis of small cell lung cancer (SCLC) with progression or recurrence after receiving **exactly one** standard firstline platinum-containing regimen (cisplatin or carboplatin). Patients must have extensive stage disease at the time of protocol entry as defined in Section 4.0 and will be stratified by platinum sensitivity status as outlined in Section 6.0. Patients with clinical evidence of recurrence do not require a confirmatory biopsy.
2. Patients may have measurable or non-measurable disease per RECIST (Section 10.1). Disease must be evident on CT scan or MRI scan. The CT from a combined PET/CT must not be used to document measurable disease unless it is of diagnostic quality as defined in Section 10.1a. All scans to assess measurable disease must have been performed within 28 days prior to registration. Non-measurable disease must be assessed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form (Form #9570).
3. Patients with known brain metastases are eligible only if he/she has been treated and stable for at least 3 months prior to study entry. Only a non-enzyme inducing anticonvulsant (e.g., Keppra) will be permitted for those patients requiring anticonvulsants. Patients must not have leptomeningeal involvement or brain stem metastases. All patients must have a pretreatment CT or MRI scan of the brain to evaluate CNS disease within 28 days prior to registration.
4. Patients may have received prior radiation therapy provided at least 21 days have elapsed since the completion of prior radiation therapy and patients must have recovered from all associated toxicities at the time of registration. Measurable or non-measurable disease must be present outside the previous radiation field or a new lesion inside the port must be present. There must be no anticipated need for concurrent radiation therapy during protocol treatment.
5. Patients may have received prior surgery provided that at least 28 days have elapsed since surgery (thoracic or other major surgeries) and patients have recovered from all associated toxicities at the time of registration. There must be no anticipated need for major surgical procedures during protocol treatment. Patients must have disease outside of the previous surgical resection area or a new lesion must be present.
6. Patients must not have had prior exposure to bevacizumab or other anti-angiogenic therapies (including but not limited to small molecule tyrosine kinase inhibitors).
7. All patients must have a Zubrod Performance Status of 0-1.
8. All patients must be 18 years of age or older
9. Patients must be offered participation in the submission and banking of specimens for future use. Examples of how specimens will be used may be found in Section 15.0 and Appendix 19.2. With the patient's consent, buffy coat, plasma and tissue will be submitted as outlined in Section 15.0.
10. Patients must have obtained the following within 28 days prior to registration:
 - a. ANC \geq 1,500/mcl,
 - b. hemoglobin \geq 10 g/dL, and
 - c. platelet count \geq 100,000/mcl.
11. Patients must have adequate renal function, as determined by the following tests: serum creatinine \leq 1.5 x the institutional upper limit of normal (IULN) OR a measured or calculated creatinine clearance \geq 60 mL/min. The serum creatinine or measured creatinine clearance level must be obtained within 28 days prior to registration
12. Patients must have a urine protein creatinine (UPC) ratio $<$ 1. For a UPC ratio \geq 1, a 24-hour urine protein must be obtained and the level must be $<$ 500 mg for patient enrollment. The urine protein used to calculate the UPC ratio must be obtained within 28 days prior to registration.
NOTE: UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm.
13. Patients must not have any evidence of active infection.
14. Patients must not have any active bleeding.

15. Patients must not have uncontrolled hypertension (either a systolic blood pressure > 150 mmHg or a diastolic blood pressure > 100 mmHg) at the time of registration. Patients with a history of hypertension controlled on anti-hypertensive medications are eligible.
16. Patients must not have a history of recent arterial embolic events such as myocardial infarction, cerebrovascular accident, transient ischemic attacks, or worsening of preexisting angina during the 6 month period leading up to trial enrollment.
17. Patients must not have a history of congestive heart failure.
18. Patients must not have a significant history of bleeding diathesis including hemoptysis (½ teaspoon of hemoptysis within 3 months) or underlying coagulopathy. Patients on chronic oral anticoagulation therapy are permitted, provided their international normalized ratio (INR) is maintained in the therapeutic range (INR 2-3). Patients on chronic therapeutic doses of low molecular weight heparins are permitted.
19. Patients must not have a prior history of encephalitis or encephalopathy of any cause.
20. Patients must not have a history of diverticulitis, gastrointestinal bleeding, or peptic ulcer during the 3 months prior to registration.
21. Patients must be willing to provide prior smoking history
22. Patients must not have known AIDS or HIV-1 associated complex or known history of immune or immunodeficiency disorders because of unknown or potential interactions of antiretroviral therapy with AVE0005. Additionally, the severely depressed immune system found in HIV-infected patients and the possibility of premature death would compromise study objectives.
23. Except for cancer-related abnormalities, patients must not have unstable or pre-existing major medical conditions.
24. Pregnant or nursing women must not participate in this trial because of the increased risk of fetal harm including fetal death from the chemotherapeutic agents. Women/men of reproductive potential must have agreed to use an effective contraceptive method.
25. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
26. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
27. At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the database.

Pre-study Parameters

1. History and physical including height, weight, performance status, blood pressure, baseline AE assessment
2. CBC with differential, serum Creatinine, PT/INR and PTT (for patients on chronic anticoagulation therapy), UPC ratio; Suggested labs: Na/ K / Ca/ Glucose/ chloride/ bilirubin/ SGOT/ SGPT/ Alk Phos/ Albumin/ BUN/ Mg/ LDH
3. X-rays and scans needed for disease assessment, Brain CT/MRI, Bone scan if clinically indicated

Treatment
AVE0005 provided.

Arm 1: AVE0005 + topotecan

Agent	Dose	Route	Days	Interval
AVE0005	6 mg/kg	IV over 1 hour	1	Q 21 days
Topotecan	4 mg/m ²	IV over 30 minutes	1, 8, 15	Q 21 days

Once cycle = 21 days

Blood pressures must be monitored weekly for the first 4 weeks.

Patients who have not progressed after four cycles may go on to subsequent treatment.

Agent	Dose	Route	Days	Interval
AVE0005	6 mg/kg	IV over 1 hour	1	Q 21 days
Topotecan	4 mg/m ²	IV over 30 minutes	1, 8	Q 21 days

Arm 2: Topotecan alone

Agent	Dose	Route	Days	Interval
Topotecan	4 mg/m ²	IV over 30 minutes	1, 8, 15	Q 21 days

Once cycle = 21 days

Patients who have not progressed after four cycles may go on to subsequent treatment.

Agent	Dose	Route	Days	Interval
Topotecan	4 mg/m ²	IV over 30 minutes	1, 8	Q 21 days