

SWOG S0635: A Phase II Trial of the Combination of OSI-774 (Erlotinib; NSC-718781) and Bevacizumab (Rhumab VEGF; NSC-704865) in Stage IIIB and IV Bronchioloalveolar Carcinoma (BAC) and Adenocarcinoma with BAC Features (AdenoBAC)

FAST FACTS

ELIGIBILITY CRITERIA

1. Patients must have biopsy-proven, incompletely resected or unresectable bronchioloalveolar carcinoma or BAC variants (adenocarcinoma with BAC features, BAC with invasive adenocarcinoma). No component of squamous carcinoma can be present in any histologic sample. NOTE: Cytology specimens, such as bronchial brushings, washings, or fine needle aspiration specimens alone are **not** acceptable for diagnosis of BAC or its subtypes.
2. Patients must be willing to provide prior smoking history as requested on the **S0635** Prestudy Form (Form #21052). Patients with BAC who are designated as "Never-Smokers" by their smoking history should be preferentially placed on trial **S0636**, which shares an identical plan, provided that this protocol is available for enrollment at the same institution.
3. Patients must have **selected** Stage IIIB (cytology-confirmed malignant pleural effusion) or Stage IV disease as defined in Section 4.0. Tumors may be multi-focal or diffuse. Recurrences of BAC in a separate lobe after prior resection within the preceding five years or multifocal lesions in more than one lobe are considered Stage IV disease.
4. Patients must have measurable and/or non-measurable disease (see Section 10.1) documented by chest CT. Measurable disease must be assessed within 28 days prior to registration. Pleural effusions, ascites and laboratory parameters are not acceptable as the only evidence of disease. 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 #848).
5. Patients must have no symptomatic brain metastases. Patients may have treated, asymptomatic brain metastases as long as they do not require steroids for symptomatic management. Patients must have EITHER a negative CT/MRI scan of the brain, OR (for patients with treated brain metastases) a stable or improved scan. These scans must be performed within 42 days prior to registration. The timeframe for having completed any radiation and/or surgery for brain metastases must conform to the 28-day rule as outlined in Sections 5.6 and 5.7.
6. Prior radiation is allowed provided that at least 28 days have elapsed since the completion of prior radiation therapy and patients 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. If the patient received palliative radiation, at least 14 days must have elapsed since completion and patients must have recovered from all associated toxicities at the time of registration.
7. Prior surgery is allowed, 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.
8. Patients must not have had a fine needle aspiration or core biopsy within 7 days prior to registration.
9. Patients may have received prior systemic chemotherapy or biologic therapy. Prior systemic therapy must have been discontinued at least 28 days prior to registration. Patients must not have received prior treatment with ZD1839 (gefitinib), OSI-774 (erlotinib), or bevacizumab. In addition, patients must not have received other targeted therapies against the EGFR or VEGF axes.
10. Patients must not have had hemoptysis $\geq \frac{1}{2}$ teaspoon within 28 days prior to registration. Patients with clinical history of pulmonary/upper respiratory hemorrhage \geq Grade 2 (per CTCAE 3.0) within 6 months or Grade 1 within 28 days prior to registration are not eligible. Patients must have no history of either thromboses or hemorrhage, including hemorrhagic or thrombotic stroke or other CNS bleeding. NOTE: The treating physician is responsible for documenting the amount of blood at hemoptysis.
11. Patients may be on stable therapeutic anticoagulation, including warfarin or low molecular weight heparin, as needed, except for those with a history of bleeding complications on anticoagulation or an inability to establish a stable therapeutic regimen for anticoagulation.
12. Patients must have the following laboratory values:
 - serum bilirubin $\leq 1.0 \times$ IULN

- SGOT or SGPT $\leq 2.5 \times$ IULN
 - alkaline phosphatase $\leq 2.5 \times$ IULN
 - ANC $\geq 1,500/\text{mcl}$
 - platelet count $\geq 100,000/\text{mcl}$
 - If liver metastases are present, SGOT/SGPT $\leq 5 \times$ IULN are allowed. If bone metastases are present, alkaline phosphatase $\leq 5 \times$ IULN is allowed.)
13. Patients must have adequate renal function, as determined by the following tests measured within 28 days prior to registration:
- serum creatinine $\leq 1.5 \times$ IULN
 - OR
 - calculated or measured creatinine clearance ≥ 50 ml/min using the following formula: Calculated Creatinine Clearance = $(140 - \text{age}) \times \text{wt (kg)} \times 0.85$ (if female) $72 \times$ serum creatinine (mg/dl)
14. Urine protein must be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For UPC ratio > 0.5 , 24-hour urine protein must be obtained and the level must be $< 1,000$ 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. UPC ratio is calculated using one of the following formulas: $[\text{urine protein}]/[\text{urine creatinine}]$ – if both protein and creatinine are reported in mg/dL $[(\text{urine protein}) \times 0.088]/[\text{urine creatinine}]$ – if urine creatinine is reported in mmol/L
15. Patients with hypertension must have hypertension controlled on medication prior to enrollment.
16. Patients must have a Zubrod Performance Status of 0 - 2 (see Section 10.5).
17. All patients must be 18 years of age or older.
18. Patients must be offered participation in correlative science studies as outlined in Section 15.0.
19. Patients must not be currently receiving or planning to receive surgery or any other nonprotocol treatment (including chemotherapy, hormonal, biologic or radiation therapy) directed at the BAC.
20. Patients must not have a serious non-healing wound, ulcer, or bone fracture.
21. 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 five years.
22. Pregnant or nursing women are not eligible to participate in this trial due to the potential teratogenic or abortifacient effects of the study drug on the fetus or nursing infant. Women and men of reproductive potential must have agreed to use an effective contraceptive method.
23. 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.

PRE-STUDY PARAMETERS

1. H&P; Wt & Performance Status
2. Disease assessment – to be performed every 6 wks. for 12 wks., then every 9 wks. until progression. Disease must be assessed using the same technique as baseline and must be documented on the Follow-up Tumor Assessment form. A response must be confirmed by a second determination at least 4 wks. after a CR or PR has been noted.
3. CBC/Diff/Platelets; Bilirubin; SGOT or SGPT; Calculated or Measured Creatinine Clearance
4. Serum Creatinine – not necessary if measured creatinine clearance is used
5. Alkaline phosphatase – Abnormalities in alkaline phosphatase levels should be appropriately followed to document the possibility of bone or hepatic metastases.
6. UPC Ration – to be performed prior to every other bevacizumab treatment
7. Albumin and LDH – suggested prestudy for Good Medical Practice
8. Tissue & blood specimens per Section 15.2
9. Chest CT – performed every 6 weeks for 12 weeks, then every 9 weeks until progression.
10. Brain CT/MRI
11. Bone Scan/PET Scan – Bone or PET Scan to be performed only if clinically indicated

12. Correlative Imaging Study – If patient is removed from protocol treatment before week 13, perform scan after discontinuation of treatment. Prestudy and follow-up CT scans should be performed with the same CT scanner (or identical brand and model) and techniques to allow for reliable comparison of response to be determined by central computer-assisted image analysis. See Section 15.1 for Radiology Review Requirements.

TREATMENT

AGENT	DOSE	ROUTE	DAYS	INTERVAL**
OSI-774	*150 mg/day	PO	1 – 21	Daily
Bevacizumab	15 mg/kg	IV infusion over 90 ± 15 minutes***	1	Q 21 days

* OSI-774 tablets are supplied as 25 mg, 100 mg, and 150 mg tablets. Tablets should be taken in the morning with up to 200 mL of water 1 hour before or 2 hours after food.

** A cycle of therapy is 21 days.

*** If no adverse reactions occur, the second dose of bevacizumab should be given over a minimum of 60 minutes. If no adverse even occurs, third and subsequent doses should be administered over a minimum of 30 minutes. Infusions should be run in a volumetric infusion device. Infusions should be run over the shortest period that is well-tolerated.