SUPPLEMENTARY MATERIAL

Supplementary Table 1. Biomarker Distribution in 255 Randomized Patients*

Biomarker	Positive Cases
EGFR mutation (exons 18-21)	33 (15%)
EGFR FISH increased copy number	
- Gene amplification	34 (16%)
- High polysomy	60 (28%)
KRAS mutation (codons 12, 13 and 61)	42 (20%)
BRAF mutation (exons 11 and 15)	5 (2%)
VEGF IHC (>100, range 0-300)	191 (89%)
VEGFR-2 IHC (>100, range 0-300)	85 (40%)
RXR - α (nucleus) IHC (>30, range 0-100)	173 (80%)
- α (cytoplasm) IHC (>200, range 0-300)	3 (1%)
- β (cytoplasm) IHC (>200, range 0-300)	12 (6%)
- β (membrane) IHC (>200, range 0-300)	0 (0%)
- γ (cytoplasm) IHC (>200, range 0-300)	23 (11%)
Cyclin D1 IHC (>10%, range 0-100)	114 (54%)
Cyclin D1 FISH amp	27 (13%)
All marker negative	2 (0.9%)
Inadequate tissue for marker analysis: (partial marker information/no marker information)	2/40 (0.9%/19%)

- **NOTE: The percentage of positive cases was calculated based on available data. The denominator may vary from marker to marker. As shown in the last row, 2 patients and 40 patients had only partial marker or no marker information due to inadequate tissue for marker analysis.**

FISH = Fluorescence in situ hybridization; IHC = Immunohistochemistry

Supplementary Table 2. Selected Toxicities (>10% in any one treatment, based on 254 pts)

	Treatment																	
	Total (N=254)				**Erlotinib (N=59)**				**Vandetanib (N=54)**				**Erlotinib + Bexarotene (N=37)**				**Sorafenib (N=104)**			
EVENT	**all grade N (%)**		**grade 3, 4, or 5 N (%)**		**all grade N (%)**		**grade 3, 4, or 5 N (%)**		**all grade N (%)**		**grade 3, 4, or 5 N (%)**		**all grade N (%)**		**grade 3, 4, or 5 N (%)**		**all grade N (%)**		**grade 3, 4, or 5 N (%)**	
Rash	123	(48.4%)	12	(4.7%)	43	(72.9%)	2	(3.4%)	17	(31.5%)	1	(1.9%)	21	(56.8%)	2	(5.4%)	42	(40.4%)	7	(6.7%)
Diarrhea	106	(41.7%)	6	(2.4%)	25	(42.4%)	2	(3.4%)	24	(44.4%)	0	(0.0%)	17	(45.9%)	1	(2.7%)	40	(38.5%)	3	(2.9%)
Pain	96	(37.8%)	17	(6.7%)	24	(40.7%)	2	(3.4%)	17	(31.5%)	3	(5.6%)	16	(43.2%)	2	(5.4%)	39	(37.5%)	10	(9.6%)
Fatigue	94	(37.0%)	19	(7.5%)	20	(33.9%)	1	(1.7%)	19	(35.2%)	3	(5.6%)	11	(29.7%)	3	(8.1%)	44	(42.3%)	12	(11.5%)
Anorexia	74	(29.1%)	6	(2.4%)	16	(27.1%)	2	(3.4%)	16	(29.6%)	2	(3.7%)	9	(24.3%)	0	(0.0%)	33	(31.7%)	2	(1.9%)
Hand/Foot Syndrome	65	(25.6%)	17	(6.7%)	.	.	.	.	.	.	.	.	3	(8.1%)	0	(0.0%)	62	(59.6%)	17	(16.3%)
Weight loss	64	(25.2%)	1	(0.4%)	10	(16.9%)	0	(0.0%)	5	(9.3%)	0	(0.0%)	9	(24.3%)	1	(2.7%)	40	(38.5%)	0	(0.0%)
Dyspnea	58	(22.8%)	17	(6.7%)	14	(23.7%)	3	(5.1%)	8	(14.8%)	3	(5.6%)	9	(24.3%)	2	(5.4%)	27	(26.0%)	9	(8.7%)
Anemia	57	(22.4%)	6	(2.4%)	5	(8.5%)	1	(1.7%)	14	(25.9%)	1	(1.9%)	10	(27.0%)	1	(2.7%)	28	(26.9%)	3	(2.9%)
Nausea	49	(19.3%)	6	(2.4%)	10	(16.9%)	1	(1.7%)	7	(13.0%)	1	(1.9%)	7	(18.9%)	1	(2.7%)	25	(24.0%)	3	(2.9%)
Hypertension	38	(15.0%)	15	(5.9%)	.	.	.	.	18	(33.3%)	7	(13.0%)	.	.	.	.	20	(19.2%)	8	(7.7%)
Hypertriglyceride	31	(12.2%)	11	(4.3%)	2	(3.4%)	0	(0.0%)	.	.	.	.	28	(75.7%)	11	(29.7%)	1	(1.0%)	0	(0.0%)
Dry skin	30	(11.8%)	1	(0.4%)	13	(22.0%)	0	(0.0%)	3	(5.6%)	0	(0.0%)	4	(10.8%)	1	(2.7%)	10	(9.6%)	0	(0.0%)
Vomiting	29	(11.4%)	1	(0.4%)	6	(10.2%)	0	(0.0%)	5	(9.3%)	0	(0.0%)	5	(13.5%)	0	(0.0%)	13	(12.5%)	1	(1.0%)
Leukopenia/neutropenia	12	(4.7%)	3	(1.2%)	1	(1.7%)	1	(1.7%)	3	(5.6%)	0	(0.0%)	6	(16.2%)	2	(5.4%)	2	(1.9%)	0	(0.0%)

Supplementary Table 3. Summary of Compliance (in %)

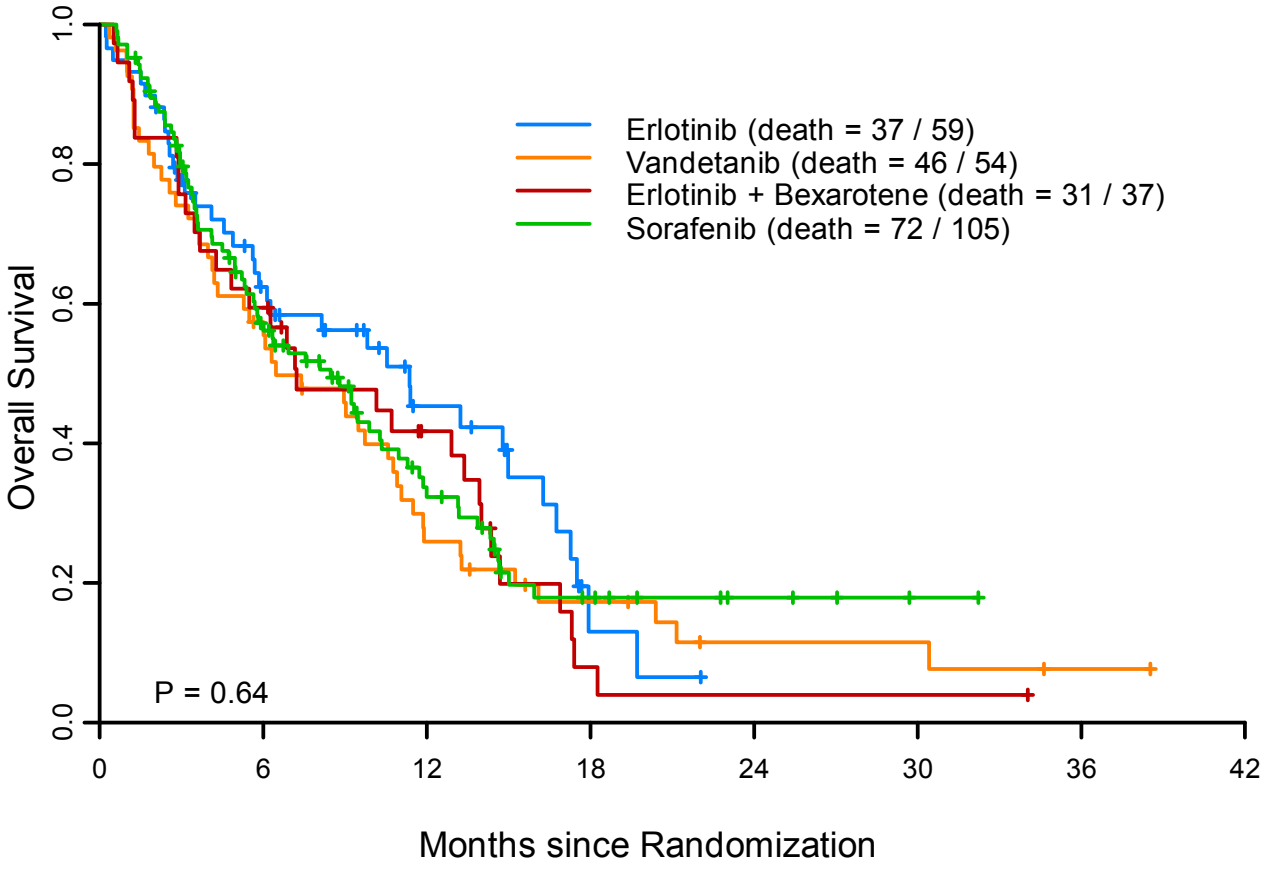
Treatment	N	Minimum	Median	Maximum	Mean	Std Dev
Erlotinib	58	80	100	100	98	4
Vandetanib	54	88	100	100	99	2
Erlotinib (in E+B)	37	66	100	100	98	6
Bexarotene (in E+B)	37	52	100	100	95	10
Sorafenib	104	61	99	100	97	5

***** The compliance% for each patient is calculated by
compliance% = (total number of tablets actually taken)/(targeted total

E: Erlotinib
B: Bexarotene

Supplementary Figure 1. Efficacy

A. Overall Survival by Treatment



Supplementary Appendix

BATTLE Executive Committee Members

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Supplementary Information: Eligibility Criteria

The following inclusion criteria must be met for entry into the study:

1. The patient has a diagnosis of pathologically confirmed NSCLC by tumor biopsy and/or fine-needle aspiration.
2. The patient has a diagnosis of either stage IIIB, stage IV, or advanced, incurable NSCLC, and failed at least one front-line metastatic NSCLC chemotherapy regimen. (Patients who have failed adjuvant or locally advanced therapy within 6 months are also eligible to participate in study).
3. The patient has uni-dimensionally measurable NSCLC.
4. Karnofsky performance status ≥ 60 or ECOG performance status 0-2
5. The patient has biopsy accessible tumor.
6. The patient has adequate hematologic function as defined by an absolute neutrophil count (ANC) ≥ 1,500/mm3, platelet count ≥ 100,000/mm3, WBC ≥ 3,000/ mm3, and hemoglobin ≥ 9 g/dL.
7. The patient has adequate hepatic function as defined by a total bilirubin level ≤ 1.5 X the upper limit of normal, and alkaline phosphatase, AST or ALT ≤ 2.5 X the upper limit of normal.
8. The patient has adequate renal function as defined by a serum creatinine level ≤ 1.5 mg/dL or a calculated creatinine clearance of ≥ 60cc/minute.
9. The patient has PT < 1.5 x upper limit of normal
10. If patient has brain metastasis, they must have been stable (treated or asymptomatic) for at least 4 weeks after radiation if treated with radiation and not have used steroids for at least 1 week. Re-imaging performed after 2 weeks, upon completion of radiation therapy.

11. The patient is ≥ 18 years of age.
12. The patient has signed informed consent.
13. The patient is eligible if disease free from a previously treated malignancy, other than a previous NSCLC, for greater than two years. Patients with a history of prior basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix are exempt from exclusion.
14. Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Childbearing potential will be defined as women who have had menses within the past 12 months, who have not had tubal ligation or bilateral oophorectomy. Should a woman become pregnant or suspect that she is pregnant while participating in this study, she should inform her treating physician immediately. The patient, if a man, agrees to use effective contraception or abstinence.
15. Subject must be considered legally capable of providing his or her own consent for participation in this study.

Exclusion Criteria

The following are grounds for exclusion from this study:

1. The patient has received prior investigational therapy, chemotherapy, surgery, or radiotherapy within 4 weeks of initiating study drug
2. The patient has undergone prior thoracic or abdominal surgery within 28 days of study entry, excluding prior diagnostic biopsy.
3. The patient has received radiation therapy to the measurable tumor within 6 months. Patients are allowed to have local irradiation for the management of tumor-related symptoms (bones,

brain). However, if a patient has active new disease growing in the previously irradiated site, the patient will be eligible to participate in the study.

4. The patient has a significant medical history or unstable medical condition (unstable systemic disease: congestive heart failure (New York Heart Association Functional Classification class II or worse), recent myocardial infarction within 3 months, unstable angina, active infection (i.e. currently treated with antibiotics), uncontrolled hypertension). Patients with controlled diabetes will be allowed. Patient must be able to undergo procedure for tissue acquisition.
5. The patient has uncontrolled seizure disorder, active neurologic disease, or neuropathy ≥ grade 2. Patients with meningeal or CNS involvement by tumor are eligible for the study if the above exclusion criteria are not met.
6. The patient is pregnant (confirmed by serum β-HCG if applicable) or is breastfeeding.
7. Any condition that is unstable or could jeopardize the safety of the patient and its compliance in the study, in the investigator's judgment.
8. The patient is actively taking herbal remedies or over-the-counter biologics (e.g., shark cartilage, high dose antioxidants).
9. Patients will be allowed to have prior biologic (i.e. VEGF, EGFR, etc.) therapy. However, the patient will be excluded from a given study if he/she has received the same therapy as the clinical trial (i.e. If a patient has been previously treated with bevacizumab, they are allowed to enroll in any of the 4 studies. If a patient has been previously treated with erlotinib, they are excluded from the clinical trials with erlotinib). In addition, if a patient has been previously treated with gefitinib (Iressa), they are excluded from the clinical trials with erlotinib.

Table A-1. Sequences of primers used for DNA polymerase chain reaction amplification for mutation analysis of *EGFR*, *KRAS* and *BRAF*

Gene/Exon	Primers Sequence 5' to 3'	Annealing Temperature in °C
	Forward: CAT GTC TGG CAC TGC TTT CC	
EGFR/18	Reverse: TAT ACA GCT TGC AAG GAC TCT G	63
	Forward: CCA GAT CAC TGG GCA GCA TGT GGC ACC	
EGFR/19	Reverse: AGC AGG GTC TAG AGC AGA GCA GCT GCC	63
	Forward: CTC CTT CTG GCC ACC ATG CG	
EGFR/20	Reverse: AGC GCA GAC CGC ATG TGA GG	63
	Forward: GAC GTG GAG AGG CTC AGA GC	
EGFR/21	Reverse: AGC ATC CTC CCC TGC ATG TG	63
	Forward: TTC ATT ACG ATA CAC GTC TGC	
KRAS/1	Reverse: GTC CTG CAC CAG TAA TAT GC	52
	Forward: CTG TAA TAA TCC AGA CTG TG	
KRAS/2	Reverse: TCC CCA GTC CTC ATG TAC TG	50
	Forward: TCC CTC TCA GGC ATA AGG TAA	
BRAF/11	Reverse: CGA ACA GTG AAT ATT TCC TTT GAT	60
	Forward: TCA TAA TGC TTG CTC TGA TAG GA	
BRAF/15	Reverse: GGC CAA AAA TTT AAT CAG TGG A	60