HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Cancer. 2017 August 01; 123(15): 2936–2944. doi:10.1002/cncr.30717.

Phase I/II study of rilotumumab (AMG 102), an HGF inhibitor, and erlotinib in patients with advanced non-small cell lung cancer

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Abstract

Background—Activation of MET and its ligand hepatocyte growth factor (HGF) are implicated in resistance to epidermal growth factor receptor (EGFR) inhibitors. This Phase I/II trial evaluated rilotumumab (anti-HGF antibody), combined with erlotinib, in patients with metastatic previously treated NSCLC.

Methods—Phase I adopted a dose de-escalation design with rilotumumab starting at 15 mg/kg intravenously every 3 weeks and erlotinib 150 mg orally daily. Phase II evaluated the disease control rate (RECIST, DCR) of the combination using a Simon 2-stage design. Biomarkers examined included 10 plasma circulating molecules associated with EGFR and MET pathways.

Results—Without indications for de-escalation, the RP2D was dose level 0. Overall, 45 response-evaluable patients were enrolled (13 squamous, 32 adenocarcinoma; 2 confirmed EGFR mutant, 33 confirmed EGFR wild-type (WT) and 7 KRAS mutant). DCR was 60% (90% CI, 47.1–71.3) in all patients. Median PFS was 2.6 months (90% CI, 1.4–2.7) and median OS was 6.6 months (90% CI, 5.6–8.9). Among EGFR WT patients, DCR was 60.6% (90% CI, 46.3–73.3), median PFS 2.6 months (90% CI, 1.4–2.7) and median OS 7.0 months (90% CI, 5.6–13.4). Elevated baseline levels of neuregulin 1 were associated with longer PFS (HR 0.41, 95% CI 0.19–0.87), while elevated amphiregulin was associated with more rapid progression (HR 2.14, 95% CI 1.48–3.08).

Conclusion—The combination had an acceptable safety profile and the DCR rate met the pre-specified criteria for success. In the EGFR WT group, DCR rate exceeded published reports for erlotinib alone. High circulating neuregulin 1 may indicate sensitivity to this combination.

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Keywords

Erlotinib; Rilotumumab (AMG 102); NSCLC; EGFR; HGF; c-MET; Neuregulin 1; Amphiregulin

Introduction

Non-small cell lung cancer (NSCLC) accounts for nearly 85% of lung cancer cases, and despite advances in treatment the 5-year survival rate remains less than 20%[1]. Erlotinib is an epidermal growth factor receptor (EGFR) oral tyrosine kinase inhibitor (TKI) first approved in 2004 for the treatment of advanced NSCLC (irrespective of histology or EGFR mutation status) after failure of at least one chemotherapy regimen. This was based on the BR.21 trial that was undertaken before EGFR mutations were established as a predictive factor[2]. A maintenance study (SATURN) examined the use of erlotinib versus placebo as maintenance in patients with non-progressive disease following first line platinum doublet chemotherapy[3]. PFS was significantly prolonged favoring adenocarcinoma histology, EGFR expression, never smokers, Asians and females [3]. Erlotinib was approved for the first line treatment of metastatic non-squamous NSCLC with a known active sensitizing EGFR mutation[4].

MET (c-MET, HGFR) is the TK receptor for hepatocyte growth factor (HGF) and it mediates pro-cancer functions including growth, invasion, metastasis, and epithelial to mesenchymal transition (EMT)[5]. Membrane overexpression, gene amplification, mutation or alternative splicing resulting in exon 14 skipping are observed in a variety of tumors[5–7]. A critical role for MET deregulation in the pathophysiology of NSCLC is established in human cell lines and patient tumor tissues[8] as well as in animal models[9]. MET amplification is also a mechanism of acquired resistance to EGFR inhibitors by activating ERBB3 (HER3) signaling to PI3K/AKT[10–13]. MET inhibition produces durable responses in MET related malignancies[6, 7] whereas combined treatment with EGFR and MET inhibitors reverses the conferred resistance to EGFR inhibitors and restores anti-tumor efficacy[12–15]. We previously demonstrated reciprocal cross-activation between MET and wild-type (WT) EGFR in NSCLC, involving downstream release of EGFR ligands initiated by HGF treatment in NSCLC cells (16, 17). EGFR activated by its ligands in turn causes a prolonged HGF-independent activation of MET (16, 17). Blocking EGFR and HGF together could reduce EGFR signaling while simultaneously inhibiting both the ligand dependent and ligand independent activation of MET (16). This combination might benefit both EGFR mutant and EGFR WT patients.

Rilotumumab (AMG 102) is a fully humanized monoclonal antibody (IgG2) that neutralizes HGF, thus preventing MET activation[18]. It can produce tumor regression in animal models[19] and administration in humans was deemed to be safe up to the highest dose tested at 20 mg/kg as monotherapy[20]. We used rilotumumab to conduct a Phase I/II combination study with erlotinib in pre-treated metastatic NSCLC.

Materials and Methods

Eligibility criteria

Patients ≥18 years old with ability to provide a written informed consent, and with recurrent or progressive advanced stage NSCLC were enrolled. They were required to have been treated with at least one and a maximum two prior chemotherapy regimens. Prior erlotinib, other EGFR TKIs or antibodies targeting EGFR were not included. Eligible patients had to meet specific safety and laboratory criteria and patients with treated brain metastasis were allowed. The University of Pittsburgh Institutional Review Board (IRB) approval was obtained for all study procedures and for informed consent documents in accordance with the declaration of Helsinki.

Study design and statistical methods

This was a phase I/II trial to evaluate the safety, recommended phase 2 dose (RP2D) and efficacy of rilotumumab in combination with erlotinib. Response Evaluation in Solid Tumors criteria (RECIST, version 1.1) were adopted for response assessment. Adverse events were assessed utilizing Common Terminology Criteria for Adverse Events (CTCAE, version 4).

For the phase I part of the trial we adopted a de-escalation design. If dose de-escalation was needed, dose reduction according to Narayana k-in-a-row design would follow setting the RP2D as the maximum below the dose associated with a 25% DLT rate (21). Rilotumumab was started at an initial dose of 15 mg/kg (dose level 0) and was planned to be de-escalated to 7.5 mg/kg (dose level -1) or 5 mg/kg (dose level -2) in case of DLT, whereas erlotinib was given at 150 mg orally daily. DLT criteria were specified in the study protocol. The study planned to enroll 8–16 patients in phase 1. In the absence of DLT among the first 8 patients, dose level 0 would be declared the RP2D. The goal of the phase 2 part was to test whether disease control rate (DCR) of 50% for erlotinib (reported in BR.21 in patients unselected for EGFR mutation)(22) could be improved by adding rilotumumab; an improvement to 70% DCR was targeted (Type I error = Type II error = 10%, power=90%). Phase 2 adopted a Simon 2-stage design where 21 patients were treated at RP2D in stage 1 and 24 in stage 2, for a total of 45 response-evaluable patients. Secondary objectives included estimates of overall and progression-free survival and exploratory correlations with patient tissue and serum.

Clinical response trend (CR-PR-SD-PD) was assessed by histology and mutation status with the Cochran-Armitage trend test. Overall and progression-free survival were estimated by the Kaplan-Meier method. Elisa assay results of 10 HGF-EGFR pathway markers were tested for association with progression-free survival. Analysis proceeded with hierarchical agglomeration clustering and by estimating proportional hazards regression on PFS. Adjustment of p values used the method of Benjamini and Hochberg.(23)

Drug administration

Rilotumumab was administered intravenously once every 3 weeks (1 treatment cycle) at a starting dose of 15 mg/kg. Intra-subject dose modifications were not allowed: a dose was

either given or held. Erlotinib was given orally daily at 150 mg. Dose modification criteria to 100 mg and 50 mg were provided.

Biomarker analyses

EGFR and KRAS mutation status was determined using CLIA-approved protocols that sequenced EGFR exons 19 and 20 and KRAS exons 12, 13 and 61. Molecular testing was either done at the University of Pittsburgh Molecular Pathology core facility or was performed by the hospital where the NSCLC diagnosis was first made. DNA sequencing was successful in 35 patients for EGFR and in 34 patients for KRAS. In other cases DNA sequencing was inconclusive or sufficient tumor material was not available. Baseline blood samples were also available from 35 enrolled subjects Blood was processed for isolation of plasma, immediately aliquoted, frozen and stored at −80 °C.

Post-treatment blood was also available on a subset of 30 subjects at cycle 2 and on 9 subjects for cycles 3, 5 and 7. Individual enzyme-linked immunosorbent assays (ELISAs) for HGF (Quantikine ELISA, R&D Systems), neuregulin 1 (NRG1) (Abcam), transforming growth factor- alpha (TGF-α) (Quantkine ELISA, R&D Systems), heparin binding-epidermal growth factor (HB-EGF) (DuoSet ELISA, R&D Systems), amphiregulin (AREG) (DuoSet ELISA, R&D Systems), vasulcar endothelial growth factor (VEGF) (Quantikine ELISA, R&D Systems), β-estradiol (Cayman Chemical) and soluble MET (ThermoFisher Scientific) were used to quantify each plasma analyte according to manufacturer's instructions. In addition IL6 and IL8 were analyzed together as a part of a multiplex Meso Scale Discovery assay. Assays were performed in duplicate and concentrations between the replicates varied by less than 10%. Mean values were used for analysis. We were unable to evaluate an association of MET protein expression in the tumors with outcome due to lack of sufficient tumor tissue.

Results

Patient demographics and disease characteristics

A total of 49 patients were screened and enrolled. Of these, four did not complete the required milestone for response evaluation, leaving 45 patients evaluable for efficacy analysis (Table 1). Thirty two patients had adenocarcinoma histology and 13 squamous. Two patients were confirmed to be EGFR mutant and 33 EGFR WT. Eight had a KRAS mutation. Ten patients had unknown EGRR mutation status; 11 patients had unknown KRAS mutation status. Enrolled patients had a median of 2 previous chemotherapy regimens.

Safety and drug administration

Phase I included 8 patients and in the absence of DLT, the RP2D was set at dose level 0 (rilotumumab 15 mg/kg every 3 weeks plus erlotinib 150 mg daily). These patients were included in phase II in accordance with the study's original design. Rilotumumab combined with erlotinib was generally well tolerated. Table 2 presents the adverse events that were considered related to the study regimen by category and severity. The median number of study treatment cycles administered was 4 (range 1–18+).

Efficacy

DCR reached 60% (90% CI 47–71) and 4 patients achieved a confirmed partial response (8.8%; 90% CI: 0.4–18.4). Partial responses ranged from 2–4 months in duration. Stable disease and objective responses were observed irrespective of NSCLC histology, EGFR or KRAS mutation status. Table 3 presents DCR across patient histologic and mutational characteristics. Among confirmed EGFR mutant patients one achieved partial response with one stable disease. Among 33 molecularly confirmed EGFR WT patients, the DCR was 60.6% (90% CI 46.3–73.3), (20/33), with one partial response. Confirmed KRAS mutant patients achieved a DCR of 87.5% (7/8), with one partial response. Median follow up for six living patients was 20 months (range 8–32 months). Median PFS of all patients reached 2.6 months (90% CI = 1.4–3.3 months) and median overall survival (OS) was 6.6 months (90% CI = 5.6–8.9 months) with probability of one year survival of 0.32 (90% CI = .22 – .46), Figure 1A and B. PFS in the molecularly confirmed EGFR WT subset was 2.6 months (90% CI = 1.4–2.7 months), and OS in this subset was 7.0 months (90% CI 5.6–13.4), Figure 2A and B.

Longer PFS among patients with high baseline plasma NRG1, and low AREG, TGFα and IL6

We next examined 10 circulating biomarkers that were selected for their association with the EGFR and MET pathways for relationship to outcome among the 35 trial participants with baseline blood. Demographics of this subset showed no significant differences compared to the total patient group. Biomarkers measured included 4 EGFR/HER ligands: AREG, HB-EGF, TGFα, and NRG1. We also measured plasma levels of HGF and soluble MET as well as four factors known to be regulated by HGF: VEGF, β-estradiol, IL6 and IL8. We examined correlations among the markers and found that TGFαwas highly correlated with both HGF (rho=0.60, P=.0002, FDR= .009) and IL8 (rho= 0.45, P = .0082. FDR= .184). NRG-1 was negatively correlated with two of the other HER ligands (rho = −.35 for AREG and rho= −.34 for TGFα, $P < 0.05$).

All patients had detectable soluble MET and HGF in plasma. At cycle 2, the HGF level increased from a median baseline of 2184 pg/ml to a median of 5027 pg/ml. Among 10 patients with measurements throughout 7 cycles, a non-linear increase that plateaued over time was observed (Supplemental Fig. 1). The elevation in HGF was consistent with a pharmacodynamic effect of rilotumumab, as shown in previous clinical results (24). Also consistent with previous results, HGF baseline plasma levels and change in HGF did not correlate with treatment response (24). Neither baseline levels nor changes in soluble MET were correlated with response to rilotumumab combined with erlotinib, also consistent with other clinical studies (24).

Baseline levels of AREG, IL6, NRG1, and TGFα showed significant associations with PFS, with false discovery rate set at < 10%. High NRG1 associated with longer PFS (HR= 0.41, CI = 0.19 – 0.87), while high AREG (HR= 2.14, CI = 1.48 – 3.08), TGFα (HR= 1.77, CI = 1.01 – 3.11) and IL6 (HR= 1.29, CI= 1.09 – 1.53) were associated with more rapid progression (Table 4). Each of these markers showed no appreciable change post-treatment, over up to seven treatment cycles (not shown). Baseline levels or changes over time of

VEGF, IL8, HB-EGF, and β-estradiol showed no significant association with PFS or other outcome measures (not shown).

Clustering of baseline markers in a heat map sorted by PFS for each patient further showed that higher NRG1 levels clustered with better PFS (Figure 3). Two distinct clusters were identified: one was based on NRG1 status while all of the other markers identified a second cluster, confirming the importance of NRG1 in association to this drug combination response. The heatmap illustrated that patients with PFS of 4 months or longer also had lower plasma levels of AREG, TGFα, and VEGF. Lower IL6, IL8, and HB-EGF also clustered with longer PFS, while HGF and soluble MET did not show this relationship.

Discussion

This is a first in human study to combine an EGFR targeted therapy with an HGF neutralizing antibody in heavily pretreated, unselected patients with advanced NSCLC. Choice of this therapeutic combination was based on preclinical data indicating c-Met as either de novo upregulated in NSCLC[5, 8, 9, 13] or as an escape mechanism to EGFR inhibition[10–12, 14] with a possible synergistic effect[15], and on observations of signaling interactions between EGFR and c-Met [16, 17].

The combination proved to be tolerable with no DLTs during phase 1. observed a DCR of 60% in all evaluable patients, as compared to 50% reported in BR.21 for erlotinib alone in an unselected population. BR.21 was enriched with patients who are more likely to have EGFR mutation (never smokers, women, Asian descent) that factored in the overall DCR. Subsequently the TITAN study, which was not enriched in these subsets, reported a 34.5% DCR in pre-treated patients unselected for EGFR mutation [25]. The EGFR mutant group had much better outcome than the WT group [25]. Additional studies enrolled only EGFR WT patients and reported DCR for erlotinib alone in the second line setting of 21.8% [26] and 26% [27]. Our study was powered to show an improvement in DCR over BR.21, and the CI achieved (47%–71%) was within the reported 50% range, but was superior to that reported in TITAN (34.5%). Erlotinib plus rilotumumab in the confirmed EGFR WT group achieved a DCR with a CI of 46%–73%, well above the best result (26%)[27] reported for erlotinib as second line therapy in EGFR WT patients. Half of our patients were treated in the third line setting, further suggesting rilotumumab added to erlotinib improved the DCR for EGFR WT patients. Both patients with an EGFR activating mutation had stable disease. Regarding patients with KRAS mutation, who are known to be resistant to erlotinib [25], 7 of 8 (87.5%) achieved DCR

We identified NRG1, a ligand for HER3, to be positively correlated with improved PFS, while ligands with preference for EGFR (TGFα, AREG, HB-EGF) were either negatively correlated with PFS or showed no relationship. Patients with high NRG1 also showed low AREG and TGFα. HER3, an EGFR family member that can dimerize with EGFR/HER1, can also be activated by MET[20] and may serve as a mediator of more prolonged signaling from both EGFR and MET. NSCLC tumors with high NRG1 and low AREG and/or TGFα may have signaling driven by HER3 activation rather than EGFR activation. These tumors may have enhanced HER family signaling resulting from EGFR/HER3 heterodimers (since

HER3 lacks a kinase and needs a dimer partner to signal), and be more dependent on HER3 to propagate MET signaling. The combination of erlotinib with rilotumumab could block both of these axes.

NRG1 was found to be associated with responses to ERRB3/HER3 inhibitory antibodies in a variety of tumor types [28, 29] and with resistance to cetuximab in colon cancer [30]. NRG1 was not independently associated with survival [29], suggesting it is predictive of therapeutic benefit rather than prognostic. Elevated plasma TGFα predicted lack of benefit to erlotinib in BR.21, while AREG was not predictive but showed association with poor prognosis [31]. Our observations are consistent with these findings. Positive AREG expression in tumor tissue was related to better survival in a retrospective study of EGFR WT patients who received erlotinib, compared to those with undetectable expression, but plasma was not analyzed [32].

Combinations of rilotumumab with other targeted therapies or chemotherapy were examined in several tumor types with promising results[33–36]. In metastatic gastric cancer epirubicin/cisplatin/capecitabine chemotherapy plus rilotumumab was tested[37, 38] and led to the initiation of 2 large, phase 3 trials in advanced, MET positive gastric cancer, examining rilotumumab with two different chemotherapy regimens. The RILOMET-1 study was stopped early based on an imbalance in deaths towards the rilotumumab plus chemotherapy arm. All statistical endpoints were also worse for patients exposed to rilotumumab with no subgroup benefit seen even in patients with ≥1+ MET expression[39]. As a result, all sponsored trials with rilotumab in gastric cancer were terminated[40].

A separate potent humanized HGF monoclonal antibody, ficlatuzumab, demonstrated synergistic activity in combination with the EGFR inhibitors erlotinib and cetuximab in preclinical NSCLC models (41). Ficlatuzumab is currently being evaluated in a phase 2 study combined with erlotinib versus erlotinib alone in previously untreated EGFR mutated NSCLC patients (NCT02318368). Onartuzumab (MetMAb), the “one-armed” MET directed monoclonal antibody advanced to a double-blind phase III trial of onartuzumab plus erlotinib versus erlotinib alone in previously treated advanced NSCLC (MET-lung) but was terminated prematurely due to lack of clinical efficacy (42). Subsequent subset analysis showed improved survival in MET-positive patients (43). In our study we were not able to conduct c-met protein expression or gene amplification correlative studies due to lack of sufficient tumor tissue. A novel MET targeting antibody targeting both ligand-dependent and –independent MET signaling, ABT-700 was well tolerated in early clinical studies and demonstrated anti-tumor activity in select patients with MET amplified tumors (44). A multitude of small molecule MET inhibitors are also being evaluated in clinical trials in combination with EGFR TKIs, including cabozantinib, crizotinib, volitinib and tivantinib. Based on our observation in the EGFR WT group of DCR greatly exceeding previous reports for erlotinib alone, ongoing and future studies of MET inhibitors in combination with EGFR TKIs should further explore activity in this population in the third line setting in patients failing first and second line chemotherapeutic and immunotherapeutic interventions. Importantly, biomarker identification and patient selection strategies to predict sensitivity to these dual-targeted studies are needed and circulating NRG1 should be further explored as a potential biomarker.

Conclusions

Patients with EGFR WT tumors achieved high disease control, and even patients with KRAS mutation, a known factor to confer resistance to EGFR inhibitors, appeared to show notable disease control (with one response). We identified NRG1, a ligand for HER3, to be positively correlated with improved PFS, supporting future validation studies as a potential of predictor of therapeutic benefit. This is in accordance with the role of HER3 as an escape mechanism through EGFR/HER3 dimerization and/or MET activation[12]. The observed DCR slightly exceeded the target based on BR.21 in unselected patients, but in the EGFR WT group the DCR greatly exceeded previous reports for erlotinib alone. Our findings are limited by the small sample size of our study but support future testing of EGFR/MET dual-inhibition in the salvage setting at least in the in the EGFR WT group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This study was supported by a grant from Amgen and partly supported by NIH award SPORE in Lung Cancer P50CA090440. UPCI shared resources that are supported in part by NIH/NCI award P30CA047904 were used for this project. An award from the V Foundation for Cancer Research also was used for this project.

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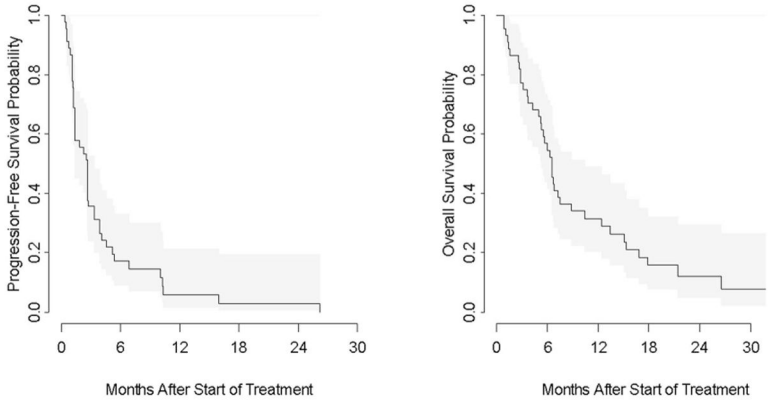

Figure 1.

All patients (A) Median PFS was 2.6 months (90% CI = 1.4–3.3 months); (B) Median OS was 6.6 months (90% CI = 5.6–8.9 months). Grey bands are 90% confidence intervals for survival probability.

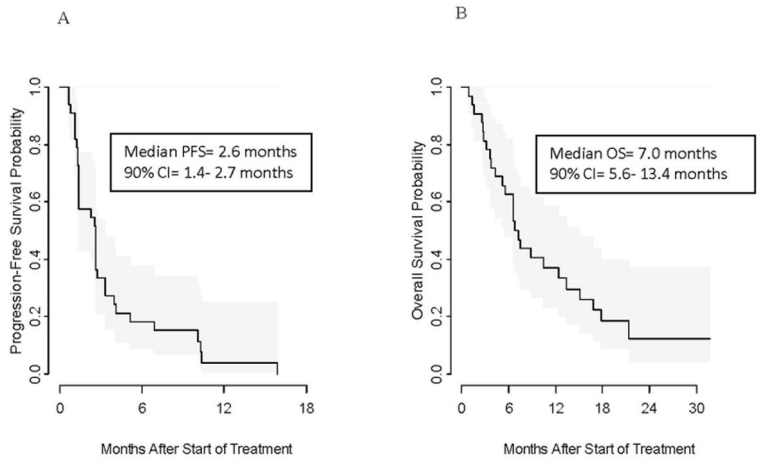

Figure 2.

Among 33 patients known to be EGFR WT (A) Median PFS was 2.6 months (90% CI = 1.4 – 2.7 months; (B) Median OS was 7.0 months (90% CI = 5.6 – 13.4 months). One patient remains alive 32 months after treatment. Grey bands are 90% confidence intervals for survival probability.

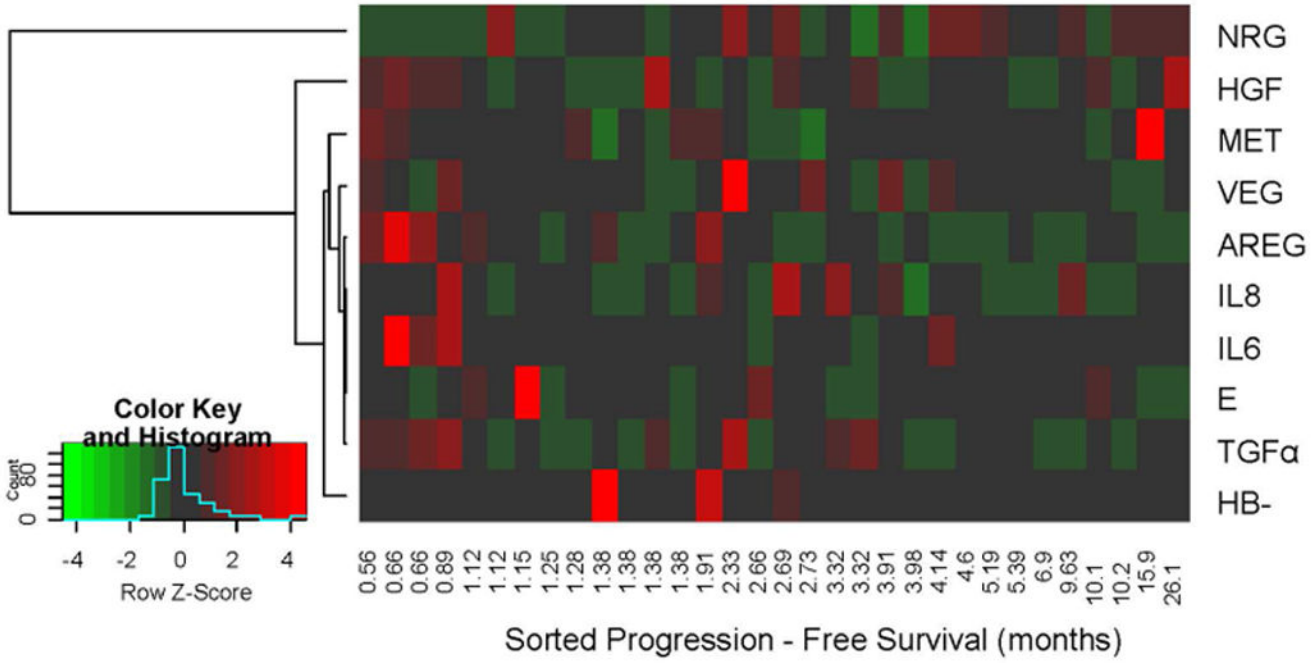

Figure 3.
Heatmap of baseline plasma markers sorted by PFS.

Table 1

Baseline Demographics and Disease Characteristics (N=45)

Characteristic	Number (%)
Gender:	
Male	20(44)
Female	25(56)
Age, mean years (range)	65(35–82)
Performance status (ECOG)	
0	22 (49)
1	20 (44)
2	3 (7)
Smoking history	
Yes	43 (96)
No	2 (4)
Histology	
Squamous	13(29%)
Non-Squamous	32(71%)
KRAS mutant (34 evaluable)	8/34 (23.5%)
EGFR mutant (35 evaluable)	2/35(5.7%)
AJCC stage IV	45(100%)
Prior lines of chemotherapy, median	2

Table 2

Adverse events (worst grade) possibly, probably or definitely related to Rilotumumab plus Erlotinib (N=45)

Type	All Grades		Grade 1		Grade 2		Grade 3		Grade 4	
	No. Pts	%	No. Pts	%	No. Pts	%	No. Pts	%	No. Pts	%
Hematologic										
Anemia	20	44	15	33	4	8	1	2	0	0
Lymphopenia	19	42	6	13	9	20	3	7	1	2
Thrombocytopenia	5	11	5	11	0	0	0	0	0	0
Thromboembolism	4	9	0	0	1	2	2	4	1	2
Integumentary										
Alopecia	5	11	4	8	1	2	0	0	0	0
Paronychia	5	11	4	8	1	2	0	0	0	0
Pruritus	5	11	4	9	1	2	0	0	0	0
Acneiform rash	25	55	17	38	7	15	1	2	0	0
Maculopapular rash	5	11	3	7	1	2	1	2	0	0
Bullous form rash	3	7	0	0	2	4	1	2	0	0
Constitutional										
Fatigue	13	28	8	17	5	11	0	0	0	0
Anorexia	10	22	7	16	3	7	0	0	0	0
Gastrointestinal/Liver										
Nausea	9	20	7	16	0	0	2	4	0	0
Vomiting	3	7	1	2	1	2	1	2	0	0
Diarrhea	22	49	13	29	4	9	5	11	0	0
Hepatitis elevated ALT/AST/AP/GGT	18	40	10	22	5	11	3	7	0	0
Oral mucositis	5	11	3	7	1	2	1	2	0	0
Neurologic										
Peripheral neuropathy	2	4	2	4	0	0	0	0	0	0
Lightheadedness/dizziness	2	4	2	4	0	0	0	0	0	0
Other Miscellaneous										
Limb edema	8	18	5	11	2	4	1	2	0	0

Type	All Grades		Grade 1		Grade 2		Grade 3		Grade 4	
	No. Pts	%	No. Pts	%	No. Pts	%	No. Pts	%	No. Pts	%
Dyspnea	3	7	1	2	1	2	1	2	0	0
Cough	3	7	1	2	2	4	0	0	0	0
Hypomagnesaemia	7	16	7	16	0	0	0	0	0	0

Table 3

Response to treatment regarding tumor histologic-mutational characteristics

Final Results						
Response		**No of patients**				
Partial Response		4				
Stable Disease		23				
Progressive Disease		18				
DCR 60% with a 90% CI of 47–71%						
Histology and Clinical Response						
		Partial Response	Stable Disease	Progressive Disease		Total
Histology	Adenocarcinoma	2	16	14		32
	Squamous	2	7	4		13
Mutational Status and Clinical Response						
		Partial Response	Stable Disease	Progressive Disease	DCR	Total
EGFR Mutation	Yes	1	1	0	100	2
	No	1	19	13	60.6	33
Cochran-Armitage Trend Test p=.069						
KRAS mutation	Yes	1	6	1	87.5	8
	No	2	14	10	61.5	26
Cochran-Armitage Trend Test p=.316						

Table 4

Hazard Ratios and Confidence Intervals for Proportional Hazards Regression of Progression-Free Survival and Baseline Serum Markers

Covariate	HR	L95	U95	Pval	Adj p
AREG	2.14	1.48	3.08	0	.0000
IL6	1.29	1.09	1.53	.0014	.0076
NRG1	0.41	0.19	0.87	.0169	.0465
TGFα	1.77	1.01	3.11	.0446	.0982
B-estradiol	1.18	0.90	1.54	.2366	.4337
VEGF	1.11	0.90	1.36	.3315	.5510
IL8	1.21	0.81	1.81	.3420	.5510
HGF	0.81	0.48	1.38	.4402	.5381
HB-EGF	1.07	.085	1.35	.5734	.6307
Sc-MET	0.94	0.70	1.25	.6531	.6531

HR = hazard ratio

L95, U95 = lower and upper 95% confidence bounds for HR

Adj.p = p value adjusted by Benjamini-Hochberg