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A Phase II Evaluation of AMG 102 (Rilotumumab) In The Treatment Of Persistent Or Recurrent Epithelial Ovarian, Fallopian Tube Or Primary Peritoneal Carcinoma: A Gynecologic Oncology Group Study

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Abstract

Purpose—This open-label, multi-institutional Phase II trial evaluated activity and safety of rilotumumab (AMG 102), a monoclonal antibody that targets HGF (hepatocyte growth factor), the ligand for the MET receptor, in women with recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancer.

Patients and methods—Women were eligible for treatment with rilotumumab if they had measurable disease, a performance status of 0, 1 or 2, previously received platinum-based therapy with a progression-free interval of <12 months or a second recurrence, and adequate bone marrow and organ function. Patients received rilotumumab 20 mg/kg IV every 14 days until evidence of unacceptable toxicity or disease progression. The study utilized co-dual primary endpoints of

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tumor response and six-month PFS to assess the efficacy of rilotumumab. Secondary endpoints included the frequency and severity of adverse events and the duration of progression-free and overall survival.

Results—Thirty-one women enrolled and received rilotumumab. All were eligible for analysis. One patient achieved a complete response (3.2%; 90% CI 0.2 – 14%), and two women had 6-month PFS (6.5%; 90% CI 1.1 – 19%). Most adverse events were grade 1 or 2, with no grade 4 adverse events. Grade 3 adverse events were gastrointestinal (4), metabolic (3) anemia (3), a thromboembolic event(1), ventricular tachycardia(1), hypotension during infusion(1) and fatigue(1). The study was stopped after the first stage of accrual.

Summary—Rilotumumab was well-tolerated, but had limited activity. The level of activity does not warrant further evaluation of rilotumumab as a single agent in patients with ovarian cancer.

Keywords

AMG 102; rilotumumab MET; HGF; scatter factor; ovarian cancer; clinical trial

Introduction

While epithelial ovarian cancer is the eighth most common cancer in women in the U.S., it is the fifth leading cause of death from cancer with 22,240 cases per year diagnosed and 14,030 deaths predicted for 2013 [1]. Most women present with advanced disease and experience recurrence. While cytotoxic therapy has improved outcomes for women with recurrent disease, ovarian cancer ultimately is likely to become resistant to chemotherapy, and most women will die of their disease [1]. Thus, there is a need for the development of new agents with activity against ovarian cancer, and there has been significant interest in the development of targeted therapeutics for women with ovarian cancer.

MET is a receptor tyrosine kinase found to be important in tumorigenesis and metastasis across a broad range of human malignancies [2,3]. It has been shown to be involved in proliferation, survival, invasion and metastasis. Upon binding by its ligand, hepatocyte growth factor/scatter factor (HGF/SF), MET is dimerized and directs cellular activity through the Ras/MAPK (mitogen-activated protein kinase) and PI3K (phosphoinositol 3 kinase) pathways, as well as the STAT (signal transducer and activator of transcription) signaling pathway [4-6]. MET can also associate with integrins, leading to Ras and PI3K pathway activation [7,8]. Epithelial to mesenchymal transitions (EMT) have been shown to play a role in ovarian carcinogenesis and metastasis [9]. HGF is a modulator of EMT and stimulates the breakdown of cell-cell adhesions between epithelial cells, thus allowing the dispersal of cancer cells and possibly increasing their invasiveness [10-14].

MET has been found to be overexpressed in human ovarian cancers and high levels of HGF/SF have been found in ascites [15-17]. Further, changes in MET expression have been linked to malignant transformation and high levels of expression of MET appear to correlate with a poor prognosis [17-20]. In tumor cells, MET signaling may be activated by ligand-dependent autocrine or paracrine mechanisms [21].

The Gynecologic Oncology Group (GOG) has investigated several targeted therapeutics for women with recurrent ovarian cancer and conducted a single-arm phase II trial of rilotumumab (AMG 102), a fully human monoclonal antibody (IgG2) against HGF that blocks binding of HGF to its receptor MET, inhibiting the HGF/MET driven activities in cells [22]. Rilotumumab has been well tolerated in early phase clinical trials, and is the first agent targeting the MET pathway to be tested in this setting [22].

Materials and Methods

Patients

Women with recurrent or persistent epithelial ovarian, primary peritoneal or fallopian tube carcinoma were eligible. Patients with carcinosarcoma were not eligible. Patients were required to have measurable disease, with at least one “target lesion” to be used to assess response on this protocol as defined by Response Evaluation in Solid Tumors (RECIST) (Version 1.1) [23]. Patients must have had one prior platinum-based chemotherapeutic regimen for the management of primary disease and could have received one additional cytotoxic regimen for the management of recurrent or persistent disease. Patients who had received only one prior cytotoxic platinum-based regimen for management of primary disease must have had a platinum-free interval of less than 12 months, or had progressed during platinum-based therapy, or had persistent disease after a platinum-based therapy. Patients must not have received any non-cytotoxic therapy for management of recurrent or persistent disease; biologic or non-cytotoxic therapy as part of the primary treatment regimen was allowed. Eligible patients had a GOG Performance Status of 0, 1, or 2 and had recovered from the effects of prior treatment. Patients must have had adequate: 1) bone marrow function (absolute neutrophil count (ANC) greater than or equal to 1,500/mcl, and platelets greater than or equal to 100,000/mcl); 2) renal function (creatinine less than or equal to $1.5 \times$ institutional upper limit normal (ULN)); 3) hepatic function (bilirubin less than or equal to $1.5 \times$ ULN, SGOT and alkaline phosphatase less than or equal to $2.5 \times$ ULN); 4) PTT (partial thromboplastin time) $1 \times$ ULN and INR $1.5 \times$ ULN; and 5) neurologic function (neuropathy (sensory and motor) less than or equal to CTCAE v3.0 grade 1). Patients must have signed an approved informed consent and authorization permitting release of personal health information, and patients of childbearing potential must have had a negative serum pregnancy test prior to the study entry and be practicing an effective form of contraception. Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer and other specific early stage and in-situ malignancies within the last five years were excluded. Also excluded were patients with an active bleeding diathesis or on oral anti-vitamin K medication (except low-dose warfarin used for catheter-related thrombosis prophylaxis), patients with a history of peptic ulcer disease, gastritis or history of gastrointestinal bleeding within the last year, or any serious intercurrent uncontrolled infections or nonmalignant medical illnesses whose control could be jeopardized by this treatment. The study protocol and informed consent documents were approved by the local IRB at each participating site.

Treatment

Eligible patients who enrolled into the study received rilotumumab 20 mg/kg IV administered over one hour for the first dose, with subsequent doses given over 30 minutes as tolerated every two weeks. Each cycle was 28 days. Patients could be treated until disease progression, withdrawal of consent or inability to tolerate further therapy.

Treatment modifications

Initial treatment modifications consisted of cycle delay and/or dose reduction as indicated below. If a patient experienced a grade 3 or 4 adverse event, AMG102 administration was postponed until the toxicity resolved to grade 1 (as defined by the Common Terminology for Adverse Events (CTCAE), version 3.0) or returned to the patient's baseline value and rilotumumab resumed at the next lowest dose level of 15 mg/kg, with a second dose reduction to 10 mg/kg in the event of a second event. No more than two dose reductions were permitted, after which the study treatment was stopped. No dose escalations or re-escalations were allowed.

Dose delays of greater than four weeks resulted in removal from study treatment, with the following particular exceptions. Non-hematologic toxicity: Grade 2 (or greater) peripheral neuropathy required a delay in subsequent therapy for a maximum of three weeks until recovered to grade 1 and a reduction of one dose level upon resumption of treatment. Grade 2 (or greater) renal toxicity (and elevations in creatinine), or grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin required a delay in subsequent therapy for a maximum of two weeks until recovered to grade 1 and a reduction of one dose level upon resumption of treatment. Patients with persistent (greater than 24 hours) grade 3 (or greater) nausea, emesis, diarrhea, or constipation in spite of optimal medical management required a delay in subsequent therapy for a maximum of two weeks until the toxicity recovered to a grade 1 and a reduction of one dose level upon resumption of treatment.

Other non-hematologic adverse events with an impact on organ function of grade 2 (or greater) required a delay in subsequent therapy for a maximum of two weeks until the toxicity recovered to grade 1 or pre-therapy baseline, and a reduction of one dose level upon resuming treatment. Hematologic toxicity: Subsequent cycles of therapy were not begun unless the ANC was ≥ 1500 cells/mcl (CTCAE v3.0 grade 1) and the platelet count was $\geq 100,000$ /mcl. Therapy was delayed for a maximum of two weeks for hematologic toxicity. Patients who did not recover adequate counts within a two week delay were removed from treatment. For first occurrence of febrile neutropenia, and/or documented grade 4 neutropenia persisting ≥ 7 days, the dose was reduced by one dose level on subsequent cycles. Patients with grade 4 thrombocytopenia were treated at a one level dose reduction. Dose modifications were not performed on the basis of uncomplicated granulocyte nadirs lasting less than seven days.

Study parameters and evaluations

Prior to commencement of treatment, patients underwent a history and physical examination, routine blood tests including blood counts and chemistries, coagulation studies

and CA-125, a urinalysis, a pregnancy test for women of child-bearing potential, an X-ray or CT scan of the chest and a CT scan or MRI of the abdomen and pelvis for tumor measurement. All blood tests and history and physical examination were repeated at the start of each cycle, with the exception of blood counts, which were performed weekly during cycle 1 and subsequently at the start of each cycle. Coagulation studies were not repeated unless clinically indicated. Imaging evaluations were repeated every other cycle. Progression free survival (PFS) was measured from study entry to disease progression, death or date of last contact; and overall survival (OS) was defined from the date of study entry until death or date of last contact. Time until treatment failure (TTF) was measured from study entry until disease progression, death, start of a subsequent therapy, or date of last contact.

Statistical endpoints

The potential activity of the drug was assessed in a two-stage design that used co-primary endpoints according to a method provided by Sill et al [24]. The primary endpoints were the dichotomous variables of tumor response and whether a patient survived progression-free for at least six months (six-month PFS). The second primary endpoint is believed to be sensitive to cytostatic or tumor stabilizing effects. Historical controls were used to determine uninteresting levels of activity and are provided in more detail by Usha et al [25]. The null hypothesis was $H_0: \pi_r = 0.10$ and $\pi_s = 0.15$ where π_r is the true probability of response and π_s is the true probability of 6-month PFS. Clinically significant improvements were at least a 15% increase in the response probability (25% or more) or a 20% increase in the probability of six-month PFS (35% or more). If the drug is capable of inducing these effects in either endpoint, then there is a desire to continue further study in a phase III trial. A study that has a 10% level of significance requires about 26 patients in each stage in order to obtain at least 90% power. Deviations from these targets were allowed for administrative flexibility. The study was designed with accrual windows from 22-29 in the first stage and a cumulative accrual of 49- 56 in the second. A study that accrued 31 patients in the first stage required at least 4 patients responding or seven patients with six-month PFS before going to the second stage. If the study attained a cumulative accrual of 53 patients at the second stage, it would have required 14 patients with six-month PFS or nine with responses before deeming the agent worthy of further investigation. Such a study would have a 52 to 59% probability of early termination under H_0 with about 92 to 93% probability of detecting activity under the alternative, depending on the level of association between response and 6-month PFS.

OS and PFS were characterized by Kaplan-Meier plots and their estimates of median times. The frequency and severity of adverse events were tabulated by organ or organ system.

Results

A total of 31 patients were enrolled in the study. Table 1 presents the characteristics of these patients. The median number of cycles was two (range 1-10) with a total of over 50 cycles of ritumumab administered during the course of the study. Twenty-eight patients discontinued treatment for disease progression. One patient stopped therapy due to toxicity,

one declined further therapy and proceeded to hospice, and one withdrew based on her physician's advice.

Rilotumumab was overall well tolerated, with no Grade 4 adverse events and very few Grade 3 adverse events. Table 2 presents the adverse events attributed to rilotumumab observed during the study. The most common adverse events were anemia in 18 patients, gastrointestinal distress in 19 patients, and local infusion reactions in 21 patients. One patient experienced Grade 3 vomiting and diarrhea that resolved within 24 hours with IV hydration and optimal medical therapy. In spite of a dose reduction at cycle two, this patient experienced a second event of grade 3 vomiting concurrent with disease progression at cycle 2. Three additional patients experienced Grade 3 vomiting or diarrhea, and there were single events of Grade 3 ventricular tachycardia, hyponatremia, hypotension and fatigue. One patient with a prior history of myocardial infarction was found to have a left ventricular aneurysm with an associated thrombus at cycle two.

All 31 patients were evaluable for efficacy. One patient achieved a complete response (3.2%; 90% CI 0.2 – 14%), and six patients experienced stable disease. There were no partial responses. Two patients had six-month PFS (6.5%; 90% CI 1.1 – 19%). Both endpoints failed to justify accrual to a second stage. The patient who had a complete response also had six-month PFS, and received a total of 10 cycles of therapy. This patient had endometrioid and clear cell histology, and had received two courses of platinum-based therapy, but recurred within six months of her second-line platinum-based therapy. The other patients who had experienced stable disease as best response all had papillary serous histology. The second patient with six month PFS had platinum resistant disease, and received eight cycles of therapy. The other patients with stable disease as best response included three patients who had received a second platinum-based regimen for their recurrence and recurred within nine months of completion of this therapy and one patient who had platinum refractory disease. See Table 3 for more information including cycles of therapy. Figure 1 presents PFS and OS curves. The median PFS was 1.84 months (90% CI 1.66 – 1.94 months). The first quartile for OS was 4.27 months (90% CI 1.91 – 5.85 months). The median survival could not be estimated at the time the data were frozen.

Discussion

The HGF/MET pathway remains an area of interest in the development of therapeutic interventions across multiple types of cancer, and there are currently several agents targeting this pathway in clinical trials. Rilotumumab was well tolerated in women with recurrent ovarian cancer, and its every-other week dosing schedule was quite feasible. While rilotumumab has had limited benefit in our patient population, or as a single agent in treating patients with other malignant diseases [24,25], it has demonstrated enhanced activity when combined with panitumumab, a monoclonal antibody that binds to the human epidermal growth factor receptor (EGFR) in patients with KRAS wild-type colorectal cancer when compared with panitumumab alone [26], suggesting that inhibition of multiple pathways may be a more effective approach to treatment of some patients with cancer. MET amplification has been proposed as a possible cause of development of resistance to EGFR inhibition [27]. Further, it is possible that the effector pathways of MET, including the Ras/

MAPK, PI3K and STAT pathways may be activated through alternative means when MET signaling is inhibited by targeting of HGF with rilotumumab, and that combination therapy may work more effectively to control disease.

Alternatively, MET may be activated through direct interaction with other cell surface receptors such as integrins or the HER (human epidermal growth factor receptor) family of receptors, and thus targeting of HGF alone may not be sufficient to inhibit MET signaling. Rilotumumab is also being evaluated in combination with cytotoxic chemotherapy in advanced carcinoma of the gastroesophageal junction, and with erlotinib in patients with advanced non-small cell lung cancer.

One of the greatest challenges in the development of targeted approaches is identifying the patients most likely to experience benefit. In our small sample size, while 25 (81%) women were diagnosed with serous carcinoma, the heterogeneity of ovarian cancer presents challenges in the development of predictive markers that may guide a targeted approach to treatment. While it is interesting that one patient did experience a complete response to treatment, the efficacy in this trial is disappointing. It is possible that further knowledge of this pathway and intersecting pathways may ultimately result in a targeted approach to therapy that utilizes MET pathway inhibition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin.* 2012; 62:10–29. [PubMed: 22237781]
2. Peruzzi B, Bottaro DP. Targeting the c-Met signaling pathway in cancer. *Clin Cancer Res.* 2006; 12:3657–60. [PubMed: 16778093]
3. Di Renzo MF, Narsimhan RP, Olivero M, Bretti S, Giordano S, Medico E, et al. Expression of the Met/HGF receptor in normal and neoplastic human tissues. *Oncogene.* 1991; 6:1997–2003. [PubMed: 1719465]
4. Benvenuti S, Comoglio PM. The MET receptor tyrosine kinase in invasion and metastasis. *J Cell Physiol.* 2007; 213:316–25. [PubMed: 17607709]
5. Comoglio PM. Pathway specificity for Met signalling. *Nat Cell Biol.* 2001; 3:E161–2. [PubMed: 11433311]
6. Maina F, Pante G, Helmbacher F, Andres R, Porthin A, Davies AM, et al. Coupling Met to specific pathways results in distinct developmental outcomes. *Mol Cell.* 2001; 7:1293–306. [PubMed: 11430831]

7. Rahman S, Patel Y, Murray J, Patel KV, Sumathipala R, Sobel M, et al. Novel hepatocyte growth factor (HGF) binding domains on fibronectin and vitronectin coordinate a distinct and amplified Met-integrin induced signalling pathway in endothelial cells. *BMC Cell Biol.* 2005; 6(1):8. [PubMed: 15717924]
8. Trusolino L, Bertotti A, Comoglio PM. A signaling adapter function for alpha6beta4 integrin in the control of HGF-dependent invasive growth. *Cell.* 2001; 107:643–54. [PubMed: 11733063]
9. Ahmed N, Thompson EW, Quinn MA. Epithelial-mesenchymal interconversions in normal ovarian surface epithelium and ovarian carcinomas: an exception to the norm. *J Cell Physiol.* 2007; 213:581–8. [PubMed: 17708542]
10. Lamorte L, Royal I, Naujokas M, Park M. Crk adapter proteins promote an epithelial-mesenchymal-like transition and are required for HGF-mediated cell spreading and breakdown of epithelial adherens junctions. *Mol Biol Cell.* 2002; 13:1449–61. [PubMed: 12006644]
11. Weidner KM, Behrens J, Vandekerckhove J, Birchmeier W. Scatter factor: molecular characteristics and effect on the invasiveness of epithelial cells. *J Cell Biol.* 1990; 111:2097–108. [PubMed: 2146276]
12. Sowter HM, Corps AN, Smith SK. Hepatocyte growth factor (HGF) in ovarian epithelial tumour fluids stimulates the migration of ovarian carcinoma cells. *Int J Cancer.* 1999; 83:476–80. [PubMed: 10508482]
13. Ueoka Y, Kato K, Wake N. Hepatocyte growth factor modulates motility and invasiveness of ovarian carcinomas via ras mediated pathway. *Mol Cell Endocrinol.* 2003; 202:81–8. [PubMed: 12770735]
14. Weidner KM, Sachs M, Birchmeier W. The Met receptor tyrosine kinase transduces motility, proliferation, and morphogenic signals of scatter factor/hepatocyte growth factor in epithelial cells. *J Cell Biol.* 1993; 121:145–54. [PubMed: 8384622]
15. Di Renzo MF, Olivero M, Katsaros D, et al. Overexpression of the Met/HGF receptor in ovarian cancer. *Int J Cancer.* 1994; 58:658–62. [PubMed: 8077049]
16. Huntsman D, Resau JH, Klineberg E, Auersperg N. Comparison of c-met expression in ovarian epithelial tumors and normal epithelia of the female reproductive tract by quantitative laser scan microscopy. *Am J Pathol.* 1999; 155:343–8. [PubMed: 10433927]
17. Corps AN, Sowter HM, Smith SK. Hepatocyte growth factor stimulates motility, chemotaxis and mitogenesis in ovarian carcinoma cells expressing high levels of c-met. *Int J Cancer.* 1997; 73:151–5. [PubMed: 9334823]
18. Wong AS, Leung PC, Auersperg N. Hepatocyte growth factor promotes in vitro scattering and morphogenesis of human cervical carcinoma cells. *Gynecol Oncol.* 2000; 78:158–65. [PubMed: 10926796]
19. Wong AS, Pelech SL, Woo MM, Yim G, Rosen B, Ehlen T, et al. Coexpression of hepatocyte growth factor-Met: an early step in ovarian carcinogenesis? *Oncogene.* 2001; 20:1318–28. [PubMed: 11313876]
20. Sawada K, Radjabi AR, Shinomiya N, Kistner E, Kenny H, Becker AR, et al. c-Met overexpression is a prognostic factor in ovarian cancer and an effective target for inhibition of peritoneal dissemination and invasion. *Cancer Res.* 2007; 67:1670–9. [PubMed: 17308108]
21. To C, Tsao M. The roles of hepatocyte growth factor/scatter factor and met receptor in human cancers. *Oncol Rep.* 1998; 5:1013–24. [PubMed: 9683803]
22. Gordon MS, Sweeney CS, Mendelson DS, Eckhardt SG, Anderson A, Beaupre DM, et al. Safety, pharmacokinetics, and pharmacodynamics of AMG 102, a fully human hepatocyte growth factor-neutralizing monoclonal antibody, in a first-in-human study of patients with advanced solid tumors. *Clin Cancer Res.* 2010; 16:699–710. [PubMed: 20068101]
23. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009; 45:228–47. [PubMed: 19097774]
24. Sill MW, Rubinstein L, Litwin S, Yothers G. A method for utilizing co-primary efficacy outcome measures to screen regimens for activity in two-stage Phase II clinical trials. *Clin Trials.* 2012; 9:385–95. [PubMed: 22811448]

25. Usha L, Sill MW, Darcy KM, Benbrook DM, Hurteau JA, Michelin DP, et al. A Gynecologic Oncology Group phase II trial of the protein kinase C-beta inhibitor, enzastaurin and evaluation of markers with potential predictive and prognostic value in persistent or recurrent epithelial ovarian and primary peritoneal malignancies. *Gynecol Oncol.* 2011; 121:455–61. [PubMed: 21414654]
26. Wen PY, Schiff D, Cloughesy TF, Raizer JJ, Laterra J, Smitt M, et al. A phase II study evaluating the efficacy and safety of AMG 102 (rilotumumab) in patients with recurrent glioblastoma. *Neuro Oncol.* 2011; 13:437–46. [PubMed: 21297127]
27. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science.* 2007; 316:1039–43. [PubMed: 17463250]
28. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Amer Statist Assn.* 1958; 53:457–81.

Progression-Free Survival and Survival

Figure 1. Kaplan-Meier progression free and overall survival curves. [28]

Table 1
Patient Characteristics and Results (n=31)

Characteristic	Category	No. of cases	% of cases
Age	40-49	4	12.9
	50-59	6	19.4
	60-69	9	29.0
	70-79	10	32.3
	80-89	2	6.5
Race	African American	4	12.9
	Hispanic	1	3.2
	White	26	83.9
Performance Status	0	18	58.1
	1	13	41.9
Site of Disease	Ovary	23	74.2
	Fallopian tube	3	9.7
	Other	5	16.1
Cell Type	Adenocarcinoma, Unsp.	1	3.2
	Endometrioid adenocarcinoma	4	12.9
	Mixed Epithelial Carcinoma	1	3.2
	Serous Adenocarcinoma	25	80.6
Grade	1	3	9.7
	2	4	12.9
	3	23	74.2
	Pending	1	3.2
Prior Chemotherapy	1 Prior Regimen	13	41.9
	2 Prior Regimens	18	58.1
Prior Radiation	No	29	93.5
	Yes	2	6.5
Prior Immunotherapy	No	30	96.8
	Yes	1	3.2
Prior Surgery	Yes	31	100.0
Stage at diagnosis	1	2	6.45
	2	2	6.45
	3	23	74.20
	4	4	12.90

Table 2

Adverse Event(AE) (n=31)

AE Category	0	1	2	3	4
White blood cell decreased	26	5	0	0	0
Platelet count decreased	27	3	1	0	0
Anemia	13	10	5	3	0
Other Investigations	24	5	2	0	0
Cardiac	30	0	0	1	0
Eye	30	1	0	0	0
Gastrointestinal	12	11	4	4	0
General and administration site	10	14	6	1	0
Infections/infestations	30	0	1	0	0
Injury/poisoning	30	0	1	0	0
Metabolism/nutrition	15	9	4	3	0
Musculoskeletal/connective tissue	25	5	1	0	0
Peripheral sensory neuropathy	24	5	2	0	0
Nervous system	26	4	1	0	0
Psychiatric	30	0	1	0	0
Renal/urinary	28	1	2	0	0
Respiratory/thoracic/mediastinal	25	3	3	0	0
Skin/subcutaneous	25	5	1	0	0
Vascular disorders	28	1	0	2	0

Table 3
Tumor Response, 6-Month PFS, Time until Treatment Failure, and Cycles of Therapy

Characteristic	Category	No. of Cases	% of Cases
Response	Complete response ¹	1	3.2
	Stable disease	6	19.4
	Increase disease	22	71.0
	Indeterminate	2	6.5
PFS > 6 Months	No	29	93.5
	Yes ¹	2	6.5
PFS to Next Line Therapy > 6 Months	No	29	93.5
	Yes ¹	2	6.5
Cycles of Treatment ¹	1	4	12.9
	2	20	64.5
	3	1	3.2
	4	3	9.7
	5	1	3.2
	8	1	3.2
	10	1	3.2

¹ Patient with complete response also had 6-month progression free survival (PFS) and 10 cycles of therapy

² Time until treatment failure (TTF) for at least 6 months. The 2 patients with 6-month PFS also had TTF > 6 months.