MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2015-0647_MOD001
Protocol Title	A RANDOMIZED PHASE II INDUCTION DISCONTINUATION TRIAL OF EMACTUZUMAB FOLLOWING PACLITAXEL AND BEVACIZUMAB IN PATIENTS WITH PLATINUM-RESISTANT, EPITHELIAL OVARIAN, FALLOPIAN TUBE OR PRIMARY PERITONEAL CANCER.
Protocol Phase	2
Protocol Version	9.0 (Institutional Version 11)
Version Date	07/18/2020
Investigational Products	Emactuzumab
Protocol PI	Anil Sood, MD
Department	Gynecologic Oncology and Reproductive Medicine
IND Sponsor	MD Anderson Cancer Center
IND #	132167

REDIRECT

(RANDOMIZED INDUCTION DISCONTINUATION TRIAL OF EMACTUZUMAB)

A RANDOMIZED PHASE II INDUCTION DISCONTINUATION TRIAL OF EMACTUZUMAB FOLLOWING PACLITAXEL AND BEVACIZUMAB IN PATIENTS WITH PLATINUM-RESISTANT, EPITHELIAL OVARIAN, FALLOPIAN TUBE OR PRIMARY PERITONEAL CANCER.

NCT 02923739

IND 132167

M.D. ANDERSON 2015-0647

Protocol Number / Version:	REDIRECT v9
Date:	18 July 2020
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Glossary Of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BP	Blood pressure
CHF	Congestive heart failure
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common toxicity criteria adverse events
CVA	Cerebrovascular accident
CVAD	Central venous access device
CXR	Chest X-ray
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
eCRF	Electronic case report form
EPO	Erythropoietin
ESF	Eligibility screening form
FBC	Full blood count
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HT	Hypertension

Glossary Of Abbreviations

IB	Investigator's brochure
ICF	Informed consent form
INR	International normalised ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent–to-treat
i.v.	Intravenous
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
MUGA	Multi Gated Acquisition Scan
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFI_{BIO}	Biological progression-free interval
PFS	Progression-free survival
PI	Principal investigator
PP	Per protocol
PR	Partial response
PS	Performance status
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SCr	Serum creatinine
SD	Stable disease
SMPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TFI	Therapy free interval
TNM	Primary tumor/regional lymph nodes/distant metastasis

Glossary Of Abbreviations

TTP	Time to tumor progression
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WBC	White blood count
WOCP	Women of child-bearing potential

SYNOPSIS OF PROTOCOL

Abbreviated Title	A Randomized Phase II Induction Discontinuation Trial of Emactuzumab following Paclitaxel and Bevacizumab in Patients with platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer
Sponsor	University of Texas MD Anderson Cancer Center
Study Phase	II
Trial Design	Prospective, open-label, randomized, induction/discontinuation, two-arm trial.
Clinical Indication	Patients with epithelial ovarian cancer (EOC), fallopian tube carcinoma (FTC) or primary peritoneal carcinomas (PPC) who have undergone an appropriate attempt at, or completed primary platinum-based therapy, as deemed by the investigator, for their initial disease.
Primary Objective	To compare the progression-free survival of patients randomized to paclitaxel plus bevacizumab or to paclitaxel, bevacizumab plus emactuzumab.
Type of control	NACT patient population
Investigational Agent	Emactuzumab
Route of administration	IV
Treatment Groups	Part 1: Safety Lead-in of Emactuzumab + Paclitaxel + Bevacizumab Part 2A: Paclitaxel + Bevacizumab Part 2B: Arm 1: Paclitaxel + Bevacizumab Arm 2: Paclitaxel + Bevacizumab + Emactuzumab
Number of Study subjects	121 Part 1: Approximately 9 patients for safety assessment. Part 2A: Approximately 112 patients will be enrolled in the induction phase Part 2B: 80 patients, 40 per arm will be randomized. A 15% drop-out rate is assumed for this study.
Estimated duration of Study	36 months
Duration of Participation	14 months

TABLE 1 SCHEDULE OF ASSESSMENTS: PART 1 SAFETY LEAD-IN

	SCREENING		TREATMENT PERIOD (1 cycle = 4 weeks) Visits every 7 ± 3 days								End of Treatment [q]	FOLLOW -UP AFTER STUDY TREATMENT TERMINATION DOES NOT PROCEED TO PART 2B)	
Cycle	- 4	-1	Cycle 1				Cycle 2 and subsequent cycles					Safety follow-up 30 days after end of treatment (± 5 days)	Survival follow-up
Study Day	-28 to 1	-7 to 1[r]	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22			
Informed consent	X												
Demographics	X												
Medical history [a]	X												
Physical examination [b]		X	X				X				X	X	
Vital signs [c]		X	X[d[	X	X[d]	X	X[d]	X	X[d]	X	X	X	
ECOG PS		X	X				X				X	X	
ECG [e]	X												
Hematology [f]		X	X	X	X	X	X	X	X	X	X	X	
Biochemistry [g]		X	X		**X[t]**		X[t]				X	X	
Coagulation tests [h]		X	X				X[t]				X		
Urinalysis [i]		X	X				X				X		
CA-125		X	X				X				X	X	
Pregnancy test [j]		X											
Tumor assessments [k]	X[k]		X[k]							X[k]	X		
Adverse events [l]	X	X	X	X	X	X	X	X	X	X	X	X	
Survival status [m]													X
Concomitant medication [n]	X		X	X	X	X	X	X	X	X	X	X	
Archival Tissue [s]	X												

PD Blood [o]			X								X		
Paclitaxel 80 mg/m^2 i.v. [p]			X	X	X	X	X	X	X	X			
Bevacizumab 10 mg/kg i.v. [p]			X		X		X		X				
Emactuzumab 1000mg i.v. [p]			X		X		X		X				

[a] Relevant medical history only. Includes confirmation of histological diagnosis.
[b] Full physical examination should be performed at screening. Subsequent physical examinations should be symptom directed.
[c] Vital signs include blood pressure, respiration rate, pulse, temperature, and weight. Height is only measured at screening.
[d] Vital signs (including supine blood pressure, respiratory rate, pulse rate and temperature) to be measured as follows on days patients receive Emactuzaumab:

- pre-infusion
- every 15 minutes until the end of Emactuzumab infusion
- every 30 minutes until the infusion line is removed.

[e] As clinically indicated. MUGA may be obtained for clinical suspicion of decrease cardiac function
[f] Hematology: perform tests as per local standard of care and clinical indication. However as a guide, this could include hemoglobin, RBC, platelet count, WBC with differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
[g] Biochemistry: perform tests as per local standard of care and clinical indication. However as a guide, this could include sodium, potassium, calcium, blood urea nitrogen (BUN), uric acid, total protein (or albumin only), alkaline phosphatase, creatinine kinase, AST/SGOT, ALT/SGPT, GGT, LDH, total bilirubin, blood glucose, creatinine.
[h] Coagulation tests: INR, aPTT. Patient receiving full dose of coumarin derivatives at baseline should have 2 consecutive screening INR measurements 1–4 days apart. INR/aPTT for the patient on (prophylactic or full) anticoagulation therapy will be checked at least before start of every chemotherapy cycle.
[i] Urinalysis: To calculate UPC ratio. 24-hour urine collection needed in the event of proteinuria ≥ +2. Proteinuria testing can be performed according to local standards.
[j] Pregnancy test (women of child-bearing potential only): Serum pregnancy test within 7 days prior to the first study treatment or within 14 days with a confirmatory urine pregnancy test within 7 days prior to the first study treatment.
[k] Baseline assessments of the pelvis and abdomen (preferably CT, or MRI in case of contrast allergy) and (by X-ray or preferably by CT-scan) of the chest. These must be performed no more than 4 weeks before the first study treatment. Patients will be assessed for disease response or progression throughout the study according to RECIST after every 8* weeks using the same imaging method as used during screening (CT or MRI or plain X-ray). Pre-cycle clearance assessments must be performed within days 23-28 of the previous cycle. Method of tumor assessment should be consistent throughout all visits and performed until disease progression. Tumor assessment will only be performed post-study treatment in the absence of confirmation of disease progression, at 8*-week intervals. If the screening assessment is completed within 30 days of Cycle 1 Day 1, the assessment does not need to be repeated.

Notes* If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be made.

[l] Follow-up on serious or study drug-related AEs. All grade 2–5 events need to be recorded in the eCRF. Only SAEs caused by protocol-mandated interventions to be collected prior to initiation of study medication.

[m] Patients will be followed for overall survival until death; immediate and subsequent treatment regimens will be recorded if it is available. Patients with complete response will be followed every 3 months for 2 years, every 4 months in the third year, then every 6 months for 2 additional years.

[n] All concomitant medication needs to be recorded in the eCRF. Only concomitant medication as per Section 4.4 must be recorded.

[o] See Table 4. . PD: Please refer to Section 5.6.

[p] Emactuzumab should be administered before bevacizumab and then paclitaxel at the first cycle and throughout subsequent cycles. See Section 3.1 for additional instructions of infusion. Treatment will continue until progressive disease (PD), unacceptable toxicity or patient request for discontinuation. If paclitaxel is discontinued due to toxicity prior to PD, bevacizumab or bevacizumab/emactuzumab should be continued until PD, toxicity or patient request for discontinuation, whichever occurs first.

[q] Should patients be taken off study at any time during treatment, scheduled cycle day assessments may replace applicable End of Treatment visit assessments.

[r] If Day 1 assessments are completed within 7 days of treatment start date, Day 1 assessments do not have to be repeated. This applies to applicable screening assessments.

[s] If archival tissue is not available, a biopsy to obtain tissue will not be necessary nor will it deter patient from eligibility. A minimum of ten (10) unstained slides are ideal.

[t] Biochemistry and coagulation tests to include Total Bilirubin, Creatinine Kinase, LDH, AST, ALT, Alkaline Phosphatase, Albumin, GGT, aPTT/INR will be performed on Day 15 of cycle 1 ONLY for management of elevated liver enzymes. Weekly monitoring for grade 2 AST/ALT and monitoring daily for grade 3 AST/ALT until the event is assessed as stable by the investigator and toxic or viral etiologies are excluded is required per protocol and as clinically indicated. Refer to Table 7 in section 6.3.9.2.2.

TABLE 2 SCHEDULE OF ASSESSMENTS PART 2A: INDUCTION TREATMENT

	SCREENING		TREATMENT PERIOD Initial Treatment Phase Paclitaxel/Bevacizumab (1 Cycle = 4 Weeks) **Visits Every 7 ± 3 Days**								FOLLOW -UP AFTER STUDY TREATMENT TERMINATION
Cycle	- 4	-1	Cycle 1				Cycle 2				End of Treatment [p]	Safety follow-up 30 days after end of treatment (± 5 days)
Study Day	-28 to 1	-7 to 1 [q]	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22		
Informed consent	X											
Demographics	X											
Medical history [a]	X											
Physical examination [b]		X	X				X				X	X
Vital signs [c]		X	X	X	X	X	X	X	X	X	X	X
ECOG PS		X	X				X				X	X
ECG [d]	X											
Hematology [e]		X	X	X	X	X	X	X	X	X	X	X
Biochemistry [f]		X	X		X[s]		X				X	X
Coagulation tests [g]		X	X		X[s]		X				X	
Urinalysis [h]		X	X				X				X	
CA-125		X	X				X				X	X
Pregnancy test [i]		X										
Tumor assessments [j]	X		X[j]							X[j]	X	
Adverse events [k]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication [l]	X		X	X	X	X	X	X	X	X	X	X
Archival Tissue [r]	X											

PD Blood [m]										X		
PD Tissue [n]		X									X	
Paclitaxel 80 mg/m^2 i.v. [o]			X	X	X	X	X	X	X	X		
Bevacizumab 10 mg/kg i.v. [o]			X		X		X		X			

[a] Relevant medical history only. Includes confirmation of histological diagnosis.
[b] Full physical examination should be performed at screening. Subsequent physical examinations should be symptom directed.
[c] Vital signs include blood pressure, respiration rate, pulse, temperature, and weight. Height is only measured at screening.
[d] As clinically indicated. MUGA may be obtained for clinical suspicion of decrease cardiac function
[e] Hematology: perform tests as per local standard of care and clinical indication. However as a guide, this could include hemoglobin, RBC, platelet count, WBC with differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
[f] Biochemistry: perform tests as per local standard of care and clinical indication. However as a guide, this could include sodium, potassium, calcium, blood urea nitrogen (BUN), uric acid, total protein (or albumin only), alkaline phosphatase, creatinine kinase, AST/SGOT, ALT/SGPT, GGT, LDH, total bilirubin, blood glucose, creatinine.
[g] Coagulation tests: INR, aPTT. Patient receiving full dose of coumarin derivatives at baseline should have 2 consecutive screening INR measurements 1–4 days apart. INR/aPTT for the patient on (prophylactic or full) anticoagulation therapy will be checked at least before start of every chemotherapy cycle.
[h] Urinalysis: To calculate UPC ratio. 24-hour urine collection needed in the event of proteinuria ≥ +2. Proteinuria testing can be performed according to local standards.
[i] Pregnancy test (women of child-bearing potential only): Serum pregnancy test within 7 days prior to the first study treatment or within 14 days with a confirmatory urine pregnancy test within 7 days prior to the first study treatment.
[j] Baseline assessments of the pelvis and abdomen (preferably CT, or MRI in case of contrast allergy) and (by X-ray or preferably by CT-scan) of the chest. These must be performed no more than 4 weeks before the first study treatment. Patients will be assessed for disease response or progression throughout the study according to RECIST after every 8* weeks using the same imaging method as used during screening (CT or MRI or plain X-ray). Pre-cycle clearance assessments must be performed within days 23-28 of the previous cycle. Method of tumor assessment should be consistent throughout all visits and performed until disease progression. Tumor assessment will only be performed post-study treatment in the absence of confirmation of disease progression, at 8*-week intervals. See Section 5.3.1.3. If stable disease is confirmed at the end of Cycle 2, then patient may proceed to Schedule of Assessments for Part 2B. Patients with progression and objective response will be taken off study. If the screening assessment is completed within 30 days of Cycle 1 Day 1, the assessment does not need to be repeated.

Notes* If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be made

[k] Follow-up on serious or study drug-related AEs. All grade 2–5 events need to be recorded in the eCRF. Only SAEs caused by protocol-mandated interventions to be collected prior to initiation of study medication.
[l] All concomitant medication needs to be recorded in the eCRF. Only concomitant medication as per Section 4.4 must be recorded.
[m] See Table 4. PD: Please refer to Section 5.6.

[n] Tumor biopsy (See Section 5.6) will be obtained no sooner than 7 days before infusion therapy. On treatment biopsy; post induction biopsy will be done for patients undergoing randomization (after 2 cycles of therapy, see Table 3), or optionally if progression occurs (End of Treatment Visit).

[o] Treatment will continue until progressive disease (PD), unacceptable toxicity or patient request for discontinuation. If paclitaxel is discontinued due to toxicity prior to PD, bevacizumab should be continued until PD, toxicity or patient request for discontinuation, whichever occurs first.

[p] Should patients be taken off study at any time during treatment, scheduled cycle day assessments may replace applicable End of Treatment visit assessments.

[q] If Day 1 assessments are completed within 7 days of treatment start date, Day 1 assessments do not have to be repeated.

[r] If archival tissue is not available, pre-treatment biopsy material does not need to be utilized for the purposes of archival tissue, nor will it deter patient from eligibility. A minimum of twenty five (25) unstained slides are ideal.

[s] Biochemistry and coagulation tests to include bilirubin, creatinine kinase, LDH, AST, ALT, GGT, Alkaline Phosphatase, and aPTT/INR will be performed on Day 15 of cycle 1 ONLY for management of elevated liver enzymes. Weekly monitoring for grade 2 AST/ALT and monitoring daily for grade 3 AST/ALT until the event is assessed as stable by the investigator and toxic or viral etiologies are excluded is required per protocol and as clinically indicated. Refer to Table 7 in section 6.3.9.2.2.

TABLE 3 SCHEDULE OF ASSESSMENTS PART 2B: RANDOMIZED TREATMENT

	Treatment Period Randomized Cohorts Arm 1 (Paclitaxel/Bevacizumab) & Arm 2 (Paclitaxel/Bevacizumab/Emactuzumab) (1 cycle = 4 weeks) **Visits every 7 ± 3 days**								End of Treatment [p]	**FOLLOW -UP AFTER STUDY TREATMENT TERMINATION**	
Week or cycle	Cycle 1				Cycle 2 and subsequent cycles					Safety follow-up 30 (± 5 days) days after end of treatment	Survival follow-up
Study day	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22			
Physical examination [a]	X				X				X	X	
Vital signs [b]	X[c]	X	X[c]	X	X[c]	X	X[c]	X	X	X	
ECOG PS	X				X				X	X	
ECG [d]											
Hematology [e]	X	X	X	X	X	X	X	X	X	X	
Biochemistry [f]	X		X[q]		X				X	X	
Coagulation tests [g]	X		X[q]		X				X		
Urinalysis [h]	X				X				X		
CA-125	X				X				X	X	
Tumor assessments [i]	X							X[i]	X		
Adverse events [j]	X	X	X	X	X	X	X	X	X	X	
Survival status [k]											X
Concomitant medication [l]	X	X	X	X	X	X	X	X	X	X	
PD Blood [m]									X[m]		
PD Tissue [n]	X								X		
Arm 1 Drug Administration [o]											
Paclitaxel 80 mg/m^2 i.v.	X	X	X	X	X	X	X	X			
Bevacizumab 10 mg/kg i.v.	X		X		X		X				

Arm 2 Drug Administration [o]											
Paclitaxel 80 mg/m^2 i.v.	X	X	X	X	X	X	X	X			
Bevacizumab 10 mg/kg i.v.	X		X		X		X				
Emactuzumab 1000mg i.v.	X		X		X		X				

[a] Subsequent physical examinations should be symptom directed.
[b] Vital signs include blood pressure, respiration rate, pulse, temperature, and weight. Height is only measured at screening.
[c] Vital signs (including supine blood pressure, respiratory rate, pulse rate and temperature) to be measured as follows on days patients receive Emactuzumab:
- pre-infusion
- every 15 minutes until the end of Emactuzumab infusion
- every 30 minutes until the infusion line is removed.

[d] As clinically indicated. MUGA may be obtained for clinical suspicion of decrease cardiac function
[e] Hematology: perform tests as per local standard of care and clinical indication. However as a guide, this could include hemoglobin, RBC, platelet count, WBC with differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
[f] Biochemistry: perform tests as per local standard of care and clinical indication. However as a guide, this could include sodium, potassium, calcium, blood urea nitrogen (BUN), uric acid, total protein (or albumin only), alkaline phosphatase, creatinine kinase, AST/SGOT, ALT/SGPT, GGT, LDH, total bilirubin, blood glucose, creatinine.
[g] Coagulation tests: INR, aPTT. Patient receiving full dose of coumarin derivatives at baseline should have 2 consecutive screening INR measurements 1–4 days apart. INR/aPTT for the patient on (prophylactic or full) anticoagulation therapy will be checked at least before start of every chemotherapy cycle. As clinically indicated (every treatment visit if patient receiving anticoagulation treatment)
[h] Urinalysis: To calculate UPC ratio. 24-hour urine collection needed in the event of proteinuria ≥ +2. Proteinuria testing can be performed according to local standards.
[i] Patients will be assessed for disease response or progression throughout the study according to RECIST after every 8* weeks using the same imaging method as used during screening (CT or MRI or plain X-ray). Pre-cycle clearance assessments must be performed within days 23-28 of the previous cycle. Method of tumor assessment should be consistent throughout all visits and performed until disease progression. Tumor assessment will only be performed post-study treatment in the absence of confirmation of disease progression, at 8*-week intervals. See Section 5.3.1.3. Patients with evidence of progression will be followed for overall survival then taken off study.
Notes* If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be made
[j] Follow-up on serious or study drug-related AEs. All grade 2–5 events need to be recorded in the eCRF. Only SAEs caused by protocol-mandated interventions to be collected prior to initiation of study medication.

[k] Patients will be followed for overall survival; immediate and subsequent treatment regimens will be recorded if it is available. Patients with complete response will be followed every 3 months for 2 years, every 4 months in the third year, then every 6 months for 2 additional years.

[l] All concomitant medication needs to be recorded in the eCRF. Only concomitant medication as per Section 4.4 must be recorded.

[m] See Table 4. PD: Please refer to Section 5.6.

[n] Pre-randomization tumor biopsy (See Section 5.6) will be obtained no sooner than 7 days before infusion therapy. If progression occurs (End of Treatment Visit), an optional biopsy may occur.

[o] Treatment will continue until progressive disease (PD), unacceptable toxicity or patient request for discontinuation. If paclitaxel is discontinued due to toxicity prior to PD, bevacizumab should be continued until PD, toxicity or patient request for discontinuation, whichever occurs first.

[p] Should patients be taken off study at any time during treatment, scheduled cycle day assessments may replace applicable End of Treatment visit assessments.

[q] Biochemistry and coagulation tests to include bilirubin, creatinine kinase, LDH, AST, ALT, GGT, Alkaline Phosphatase, and aPTT/INR will be performed on Day 15 of cycle 1 ONLY for management of elevated liver enzymes. Weekly monitoring for grade 2 AST/ALT and monitoring daily for grade 3 AST/ALT until the event is assessed as stable by the investigator and toxic or viral etiologies are excluded is required per protocol and as clinically indicated. Refer to Table 7 in section 6.3.9.2.2.

TABLE 4. PD SCHEDULE OF ASSESSMENTS (PART 1 AND PART 2)

Time point	Sample Type		
			PD Blood
Part 1 *(Paclitaxel, Bevacizumab, Emactuzumab)*			
Cycle 1 Day 1 ***Pre-dose (w/in 4 hours pre-infusion)***			**X**
Cycle 3 Day 1 ***Pre-dose (w/in 4 hours pre-infusion)***			**X**
Cycle 5 Day 1 ***Pre-dose (w/in 4 hours pre-infusion)***			**X**
End of Treatment			**X**
Part 2A *(Paclitaxel, Bevacizumab)*			
Cycle 2 Day 22 *Pre-dose (w/in 4 hours pre-infusion)*			**X**
Part 2B Arms 1 & 2 *(Paclitaxel, Bevacizumab) or (Paclitaxel, Bevacizumab, Emactuzumab)*			
Cycle 3 Day 1 *Pre-dose (w/in 4 hours pre-infusion)*			**X**
Cycle 5 Day 1 *Pre-dose (w/in 4 hours pre-infusion)*			**X**
End of Treatment			**X**

;; PD = pharmacodynamic

1. BACKGROUND AND RATIONALE

1.1 Background – Ovarian Cancer

Epithelial ovarian cancer, along with primary peritoneal carcinoma and fallopian tube carcinoma, is the fifth most common cause of cancer-related death in women in many developed countries.[1] It is also the gynecological malignancy with the highest mortality rate.[1,2] Despite improvements in the treatment of

ovarian cancer, increases in OS have been modest [3,4] and as such, mortality remains high. This is partly due to the fact that ovarian cancer is frequently not diagnosed until it has progressed to an advanced stage. Ovarian cancer is considered a chemo-responsive neoplasm, with initial response rates to systemic chemotherapy exceeding 80% when integrated with primary cytoreductive surgery.[5] Despite this, over 50% of women diagnosed with epithelial ovarian cancer eventually go on to die from their disease.[6] Major trials published over the past 15 years report that the median PFS for patients with advanced disease ranges between 16 and 23 months while the median OS lies between 31 and 65 months.[7-11]

The majority of patients who achieve a CR with first-line chemotherapy ultimately develop recurrent disease. These patients can be subdivided into platinum-sensitive or platinum-resistant groups.[12] Platinum-sensitive patients have been principally defined as those in whom disease has recurred more than 6 months after cessation of initial platinum-containing chemotherapy.[12] Platinum-based therapies are typically used to retreat these patients, in light of clinically meaningful responses observed in these patients following a second platinum-based treatment. [13] Currently, there is no optimal treatment strategy for platinum-resistant patients whose disease recurs within 6 months of completing initial platinum-based chemotherapy.[12,14] Despite a wide range of available treatments, prolonged survival has not been shown in this setting, and ORR is generally less than 20%.[12,15] As resistant-disease is not curable, the goals of treatment for these patients include palliation of symptoms, prolonged survival and improvements in quality of life.[13,15,16]

Platinum-resistance is therefore a significant clinical problem for which improved treatment regimens are needed. In this regard, molecular targeted therapeutic agents herald a new era for cancer treatment. In the setting of epithelial ovarian cancer, a growing body of evidence supports the use of anti-angiogenic agents in combination with chemotherapies.[17] In particular, bevacizumab (Avastin®), a monoclonal antibody targeted against the pro-angiogenic vascular endothelial growth factor (VEGF), holds significant therapeutic potential.

1.2 Chemotherapies for platinum-resistant ovarian cancer

Platinum-resistant ovarian cancer is non-curable and so symptom management, delayed disease progression and improvement in both quality and length of life are the primary treatment objectives.[13,15,16, 62] Patients are often treated with sequential lines of single-agent chemotherapy. Although taxanes are now routinely administered alongside the platinum-containing compound in initial therapy, this need not preclude taxane use following disease recurrence.[18,19] Other commonly used agents include topotecan and pegylated liposomal doxorubicin (PLD).

1.2.1 Taxanes

Taxanes such as docetaxel and paclitaxel are cytotoxic agents that induce cell cycle arrest by inhibiting tubulin depolymerization and therefore stabilising microtubules.[20] Following the demonstration of superior survival with paclitaxel plus cisplatin over cyclophosphamide plus cisplatin in first-line therapy, taxane/platinum combinations have become a standard of care for initial treatment.[9,29] For this reason, most platinum-resistant patients have also been exposed to taxanes.[30] However, the mechanisms of platinum and taxane resistance are different: therefore patients resistant to platinum may respond to second-line taxanes, even if included in their initial regimen.[18,21] Furthermore, cross-resistance to

paclitaxel is incomplete.[22,23] As such, paclitaxel is considered to be a potentially active agent for the treatment of platinum-resistant disease.[2, 62]

In the setting of relapsed disease, paclitaxel is typically administered at 175 mg/m^2 as a 3-hour infusion every 3 weeks.[24,25] In a randomized trial of platinum-resistant patients, paclitaxel was associated with an ORR of 17%, median duration of response of 6 months and median OS of around 9 months.[26] Major AEs include severe neutropenia (grade 4 rates up to 23%) and neurotoxicity (in up to 42% of patients).[16,25,27]

In resistant disease, two Phase II studies have been conducted in which paclitaxel was administered on a weekly schedule. Markman et.al. reported the results of the first study where 53 patients received paclitaxel 80mg/m^2 once every 7 days.[18] Of the 36 patients with measurable disease, 25% experienced an objective response. The median time to progression was 24 weeks and the median overall survival was found to be 58 weeks. In terms of safety, the treatment regimen was found to be reasonably well tolerated with only 5 patients needed to be discontinued due to toxicity (4 because of peripheral neuropathy and 1 due to painful fingernail beds).

Building upon the findings, another Phase II study was conducted by the same group.[19] 48 patients were enrolled into a study investigating the same 80mg/m^2 weekly paclitaxel dose. By contrast to the first trial, this study allowed patients (following an initial 12 weeks of dosing) to be treated for 3-weeks, with a 1 week break. In this chemo-resistant population, the objective response rate was 20.9%. As anticipated, the most common toxicity was neuropathy (21%) and grade 2 and 3 neurotoxicity (4%).

Most recently, there are emerging data indicating that weekly paclitaxel dosing schedule may be more effective and less toxic than standard paclitaxel dosing. An ongoing Phase III trial in Japan called NOVEL[28] compares the PFS in patients with stage II–IV epithelial ovarian cancer treated with first-line carboplatin plus standard paclitaxel (3-week schedule) versus carboplatin plus a weekly paclitaxel (80 mg/m^2) regimen. An interim analysis revealed that while toxicities were similar in both groups, there was a markedly improved PFS for the weekly paclitaxel/carboplatin arm (27.9 months) compared with the standard schedule (17.1 months) (P=0.0014). The findings from the NOVEL trial are consistent with previous Phase II trials showing activity of weekly paclitaxel (80 mg/m^2 i.v.) in patients with platinum- and paclitaxel-resistant ovarian cancer.[18,19] In light of the findings from the NOVEL study, weekly paclitaxel may become more widely used in daily clinical practice.[62]

1.2.2 Bevacizumab

For detailed background information, please refer to the latest bevacizumab Investigators' Brochure.

The addition of bevacizumab to chemotherapy has been shown to improve PFS and/or OS in a series of large, randomized Phase III clinical trials in a wide range of tumor types, including metastatic colorectal cancer,[44-47] non-small cell lung cancer,[48] locally recurrent or metastatic breast cancer[49-50] and metastatic renal cell carcinoma[51,52], as well as, ovarian cancer. See Figure 1for a summary of the randomized phase III trials of bevacizumab in ovarian cancer.

Figure 1: Summary of Phase III Trials Using Bevacizumab in Women with Ovarian Cancer.

Study	Setting	N	Treatment Arm	PFS (median, months)	PFS-HR (95% CI)	OS (median, months)	OS-HR (95% CI)
GOG-218	Front-line & Maintenance	18	I: Paclitaxel + Carboplatin + Placebo; Placebo Maintenance II: Paclitaxel + Carboplatin + Bevacizumab; Placebo Maintenance III: Paclitaxel + Carboplatin + Bevacizumab; Bevacizumab Maintenance	10.3 11.2 14.1	---------- 0.91 (0.8-1.04) 0.72 (0.63-0.82)	39.3 38.7 39.7	---------- 1.036 (0.83-1.3) 0.92 (0.73-1.15)
ICON7	Front-line and Maintenance	15	I: Paclitaxel + Carboplatin II: Paclitaxel + Carboplatin + Bevacizumab; Bevacizumab Maintenance	17.4 19.8	---------- 0.87 (0.77-0.99)	58 58.6	---------- 0.85 (0.69-1.04)
AURELIA	Recurrent, Platinum-Resistant	36	I: Chemotherapy (paclitaxel-weekly, topotecan-daily x 5 or weekly, PLD) II: Chemotherapy + bevacizumab	3.4 6.7	---------- 0.48 (0.36-0.6)	13.3 16.6	---------- 0.85(0.66-1.08)
OCEANS	Recurrent, Platinum-Sensitive	48	I: Gemcitabine + Carboplatin + Placebo (combination and maintenance) II: Gemcitabine + Carboplatin + Bevacizumab (combination and maintenance)	8.4 12.4	---------- 0.48 (0.39-0.61)	32.9 33.6	---------- 0.95 (0.77-1.18)
GOG-213	Recurrent, Platinum-Sensitive	67	I: Paclitaxel + Carboplatin II: Paclitaxel + Carboplatin + Bevacizumab; Bevacizumab maintenance	10.4 13.8	---------- 0.61 (0.52-0.72)	37.3 42.2	---------- (0.83 (0.68-1.005)

PFS: Progression-Free Survival; OS: Overall Survival; HR: Hazard Ratios

1.2.2.1 AURELIA: bevacizumab in platinum-resistant ovarian cancer[62]

Patients presenting with platinum-resistant recurrent ovarian cancer are usually treated with single-agent chemotherapy; there are many acceptable options with previous phase III trials failing to demonstrate a clear “winner”. Bevacizumab, a monoclonal antibody targeting VEGF, has been extensively studied in ovarian

cancer, and has clinical activity as a single agent and in combination with platinum-based chemotherapy both in the front-line and in recurrent platinum-sensitive settings. AURELIA was the first randomized phase III trial combining bevacizumab with chemotherapy in platinum-resistant ovarian cancer.[62] Eligible patients had measurable/assessable disease, progressing within 6 months of completing platinum-based therapy. Patients with refractory disease, history of bowel obstruction, or more than two prior anticancer regimens were ineligible. After investigators selected chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan), patients were randomly assigned to single-agent chemotherapy alone or with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks, depending on the regimen) until progression, unacceptable toxicity, or consent withdrawal. Crossover to single-agent bevacizumab was permitted after progression with chemotherapy alone. The primary end point was progression-free survival (PFS) by RECIST. Secondary end points included objective response rate (ORR), overall survival (OS), safety, and patient-reported outcomes. The PFS hazard ratio (HR) was 0.48 (95% CI, 0.38 to 0.60; unstratified log-rank $P < 0.001$) representing a median PFS of 3.4 months with chemotherapy alone to 6.7 months with bevacizumab-containing therapy. RECIST ORR was 11.8% versus 27.3%, respectively ($P < 0.001$). The OS HR was 0.85 (95% CI, 0.66 to 1.08; $P = .174$; median OS, 13.3 versus 16.6 months, respectively). Grade 2 or higher hypertension and proteinuria were more common with bevacizumab. GI perforation occurred in 2.2% of bevacizumab-treated patients versus 0 in the chemotherapy treated patients. Adding bevacizumab to chemotherapy statistically significantly improved PFS and ORR; the OS trend was not significant. No new safety signals were observed.

1.2.2.2 The Immune contribution to angiogenesis escape

Numerous studies have highlighted the association between inflammation and tumor progression [21,22]. Tumor-associated macrophages (TAMs) represent a major inflammatory component of the tumor stroma and are associated with cancer progression and resistance to antiangiogenic therapy[23,24].(See Figure 2) Cytokines in tumor microenvironment polarize TAMs toward an M2 phenotype, marked by increased expression of IL-10, TGFβ, VEGF, MMPs and other cytokines that suppress adaptive immunity and stimulate metastasis and angiogenesis[25,26]. In addition, TAMs accumulate in hypoxic regions of tumors and hypoxia resulting from antiangiogenic therapy has been associated with increased TAM infiltration[27]. It has recently been shown that targeting tumor vasculature with lower vascular-normalizing doses of an anti-VEGFR2 antibody, as opposed to high antivascular/antiangiogenesis doses, can polarize TAMs from an immune inhibitory M2 phenotype to an immune stimulatory M1 phenotype that may be more effective with other anticancer therapies[28]. *In vivo* studies have shown that depleting peritoneal macrophages/TAMs inhibits ascites and decreases tumor progression and angiogenesis[29]. Zoledronic acid (ZA) is clinically used to prevent or treat osteoporosis and also impairs M2 polarization of macrophages. Depletion of macrophages by ZA in combination with sorafenib significantly inhibited tumor progression, tumor angiogenesis and metastasis in a hepatocellular carcinoma murine model compared to treatment with sorafenib alone[30]. CSF-1R tyrosine kinase inhibitors target TAMs and alter macrophage polarization[31]. Targeting CSF-1R also inhibits tumor angiogenesis

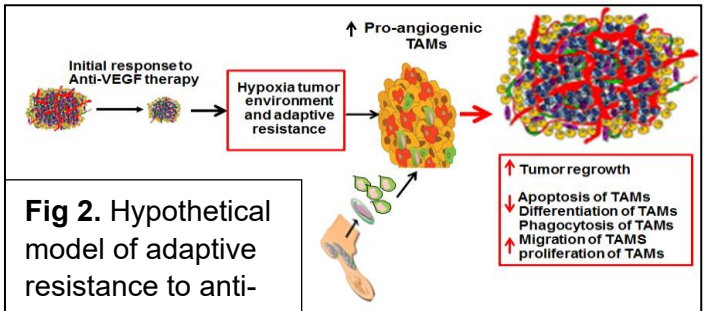


Fig 2. Hypothetical model of adaptive resistance to anti-VEGF therapy.

associated with decreased expression of proangiogenic genes. The combination of a CSF-1R inhibitor with an anti-VEGFR-2 antibody synergistically suppressed tumor growth and angiogenesis, suggesting that combination therapy may inhibit tumor growth better than either approach alone[32].

1.2.3 Emactuzumab

Emactuzumab is a recombinant, humanized monoclonal antibody (mAb) of the immunoglobulin (Ig) IgG_1 subclass directed against CSF-1R expressed on macrophages. It binds to the membrane proximal extracellular domains D4 and D5, which constitute the receptor dimerization interface. RO5509554 blocks CSF-1– and IL-34–mediated as well as ligand-independent activation of the receptor, which results in induction of apoptosis of M2-like macrophages differentiated in vitro in the presence of CSF-1 while sparing the M1-like GM-CSF–differentiated macrophages. CSF-1–differentiated macrophages have been shown to suppress T cell activation in an in vitro co-culture assay (Ries et al. 2014). In human breast cancer tissue, M2-like (CD68 +/CD163 +) macrophages and CSF-1R–expressing macrophages are co-localized. In the cynomolgus monkey, 13 weeks of treatment with RO5509554 reduced CD163 positive macrophages in the liver and colon but not in the alveolar macrophages.

Emactuzumab is a first in class, novel, CSF-1R inhibitor with nanomolar affinity for CSR-1R and has demonstrated single agent phase I activity in solid tumors. (Investigator's Brochure) Combination therapy with weekly paclitaxel did not produce new safety signals at the recommended phase II dose.

A dose dependent decrease in dermal macrophages was observed in surrogate skin biopsies from 200 mg onwards reaching plateau at ≥ 900 mg doses for monotherapy and in combination with paclitaxel. A decrease in TAMs (Tumor Associated Macrophages) from paired tumor biopsies was also observed. Such a decrease did not show a clear dose dependent trend, most likely due to the higher variability observed in the tumor biopsies and the limited number of patients in each dose cohort. In summary, the PK/PD analysis from the Phase I dose escalation study indicated that a dose of 1000 mg given Q2W would achieve the required ≥90% target saturation resulting in depletion of macrophages, without altering the safety/tolerability profile. Based upon this information a dose of 1000 mg Q2W was recommended to be administered for Part II of the study in monotherapy for all indications and in combination with paclitaxel 80 mg/m^2.
Please see Investigator's Brochure for more details on emactuzumab.

1.2.3.1 Safety

Preliminary safety data were available for a total of 205 at the clinical cutoff date of 01 November 2015.

Emactuzumab doses of up to 3000 mg have been administered to patients as monotherapy and up to 2000 mg in combination with fixed-dose paclitaxel. Emactuzumab was generally well tolerated.

The maximum tolerated dose (MTD) was not reached in either study arm based on the predefined incidence of dose-limiting toxicities (DLTs). In Arm A (emactuzumab monotherapy), 1300 AEs were reported in 147 patients. The most common adverse events (AEs) were asthenia, pruritus, periorbital edema, and peripheral edema. The majority of AEs were Grade 1 or 2. One Grade 5 (fatal) AE of large intestinal obstruction due to progressive disease, one Grade 5 (fatal) AE of cerebrovascular ischemia, and one Grade 3 AE of confusional state due to progressive disease with a fatal outcome were reported; neither was considered as related to study treatment. There were 50 serious AEs (SAEs) reported, with 18 related SAEs. A total of 16 patients were withdrawn from treatment in
Arm A.

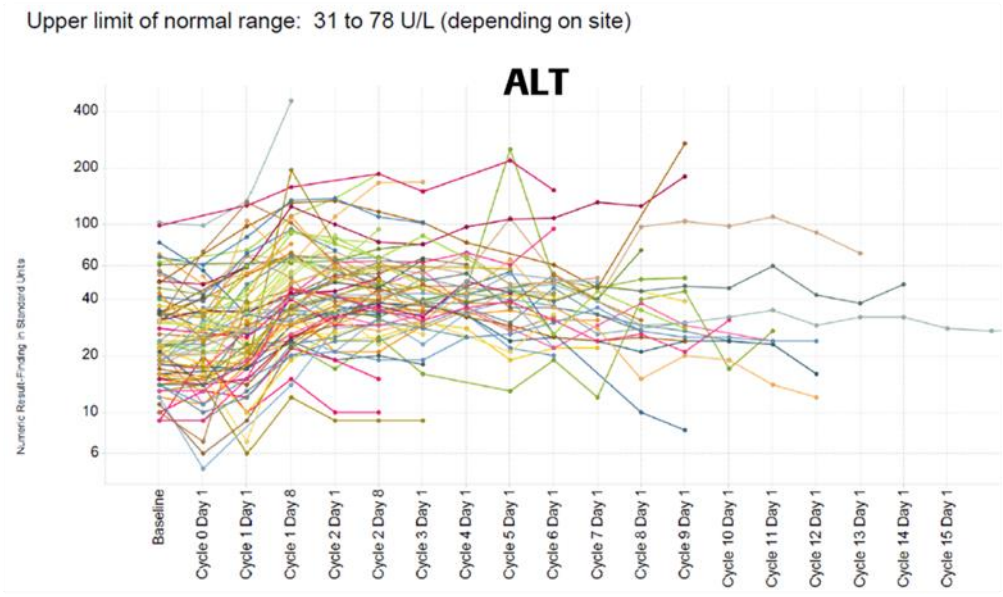
In Arm B (emactuzumab in combination with paclitaxel), 793 AEs were reported in 54 patients. The most common AEs were asthenia, periorbital edema, anemia, and nausea. As in Arm A, the majority of AEs were

Grade 1 or 2. There were one Grade 5 (fatal) AE of large intestine perforation, considered as related to treatment and a DLT, and one Grade 5 (fatal) AE of malignant bowel obstruction, considered as not related to treatment, reported in Arm B. There were 46 SAEs reported, with 16 related SAEs. A total of 6 patients were withdrawn from treatment in Arm B.

There were 19 deaths (11 in Arm A and 8 in Arm B) reported in the study, with progression of the underlying disease considered to be the cause of 17 deaths. One patient in Arm A died due to unrelated cerebrovascular ischemia. The cause of death for one patient in Arm B was metastatic progressive disease and the AE of large intestine perforation, considered as related to treatment and a DLT. However, it could not be ruled out that the perforation was due to the underlying disease in this patient with known and progressive peritoneal carcinomatosis.

Results from BP27772 EIH: Emactuzumab single agent

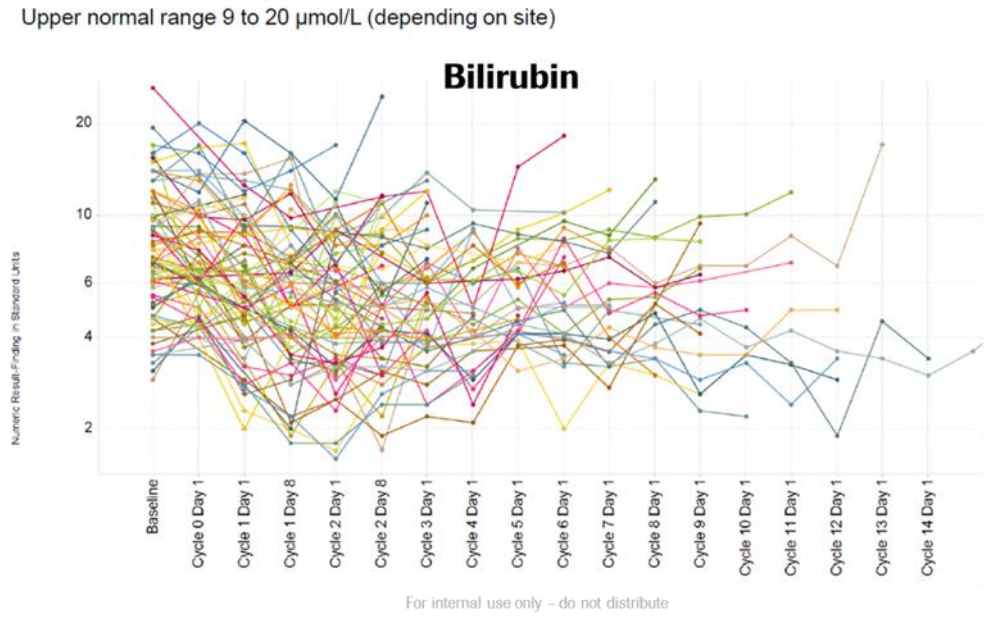
Elevation of ALT is observed with Emactuzumab treatment



None of the patients developed clinical evidence for liver cell damage or functional impairment (liver biopsies in Emactuzumab EIH study showed normal parenchyma)

Results from BP27772 EIH: Emactuzumab single agent

Bilirubin levels remain within normal ranges in the absence of clinical evidence for liver toxicity



See the emactuzumab Investigator's Brochure for details on the clinical safety of emactuzumab.

1.2.3.2 Efficacy

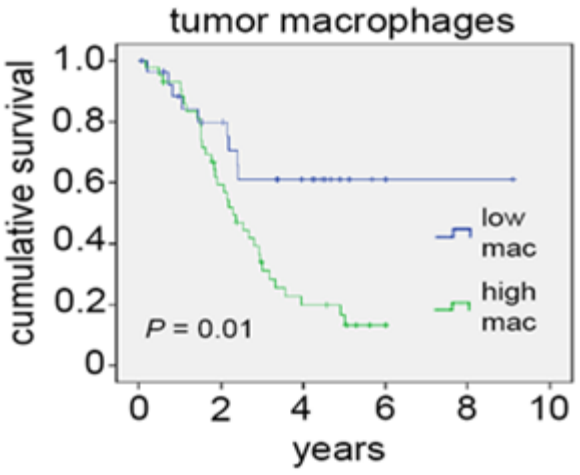
A total of 205 patients had been assessed for tumor response at the time of the clinical cutoff date of 01 November 2015. Of the 205 patients enrolled in the study at this date, 167 patients had been evaluated for tumor responses according to RECIST v1.1.

Of the 167 evaluable patients, 2 of 47 patients with pigmented villonodular synovitis [PVNS] in Arm A (emactuzumab monotherapy) had a best timepoint response on study of CR, whereas 35 of 47 patients with PVNS in Arm A and 7 of 46 patients with locally advanced and/or metastatic ovarian or breast cancer in Arm B (in combination with paclitaxel) had a best timepoint response on study of PR; PVNS is a reactive inflammatory disorder and clonal neoplastic proliferation with a chromosomal translocation CSF-1 COL6A3 that leads to overexpression of CSF-1 in malignant cells. A total of 53 patients had stable disease while on study (10 of 47 patients with PVNS in Arm A, 19 of 74 non-PVNS patients in Arm A, and 24 of 46 patients with locally advanced and/or metastatic ovarian or breast cancer in Arm B).

1.3 Study rationale

Relapsed ovarian cancer is not currently curable. Careful investigation of novel agents in this cohort has reliably extended PFS without a clear impact on OS. Indeed, many patients ultimately develop progressive disease on bevacizumab. The mechanisms for this clinical phenotype are not precisely known but likely involve a multifactorial process of endogenous and exogenous growth factors, stromal and endothelial alteration and immunosurveillance suppression. We have extensively studied this latter effect in preclinical

models by inducing a resistant state in *in vivo* orthotopic murine models under continuous anti-VEGF therapy and have identified multiple adaptive changes, including infiltration of CD11b+F4/80+macrophages (TAMs) and CD11b+Gr-1+ (MDSCs). These induced alterations were strongly associated with increasing vessel count and density suggesting that therapy targeted to these adaptive responses might induce more robust anti-tumor activity. We formally tested this hypothesis by treating anti-VEGF resistant murine orthotopic ovarian cancer xenografts with zoledronic acid and liposomal clodronate while continuing anti-VEGF therapy and demonstrated restored clinical response. Clinically, elevated tumoral macrophages (CD68+, High >15/hpf) are associated with poor outcome in women with ovarian cancer. (see Figure).



Overall Survival is adversely impacted by elevated intratumoral CD68+ macrophages in ovarian cancer patients.

We propose a clinical study in recurrent platinum-resistant ovarian cancer patients that directly evaluates the ability of TAM-targeting by emactuzumab to overcome induced angiogenesis resistance following exposure to bevacizumab. This novel trial design will enable evaluation of clinical efficacy endpoints, as well as, microenvironment adaptive changes in response to combination paclitaxel/bevacizumab. We will also generate correlative dynamic imaging and develop a significant safety database to draw upon for future clinical investigation and drug development. In light of the recent approval of bevacizumab in combination with chemotherapy, the current trial design provides a unique opportunity to clearly understand one aspect of adaptive resistance in the tumor microenvironment and evaluate highly effective targeted adjuvants to overcome this response to therapy.

The rationales for the study design and dose selection are described in detail in sections 3.1.1 and 3.1.2.

2. OBJECTIVES

2.1 Primary

- Part 1: To evaluate the safety of administration of paclitaxel, bevacizumab and emactuzumab over 4 weeks.
- Part 2B: To compare the progression-free survival (PFS) of patients with stable disease following Part 2A randomized to paclitaxel plus bevacizumab or to paclitaxel, bevacizumab plus emactuzumab.

2.2 Secondary objectives

- To estimate the progression-free survival (PFS) of the treatment arms.
- Objective response rate (ORR)
  - by RECIST and CA-125 response criteria (“responders”).
  - by RECIST only (“RECIST responders”).
  - by CA-125 response criteria only (“CA-125 responders”).
- Biological progression-free interval (PFI_{bio})
  - by serum CA-125 assessed according to the GCIG criteria (http://www.gcig.igcs.org/CA-125.html).
- Overall survival (OS).

- Safety and tolerability.

2.3 Exploratory objectives

- To assess the utility of surrogate biomarkers and the anti-tumor response to therapy with the combination treatment of bevacizumab and emactuzumab, we will draw 20 ml blood for plasma markers (VEGF, VEGFR, IL6, IL8, FGF, PDGFAA, CSF1, and IL34) and other chemokines identified by secretome proteomics) and potential exosomal markers (M2-like markers VEGFR1-3, CD11b +CD68, CD11b+CD14/CD15/CD33,CD11b+CD11c,MHCII),priortoinitiationof paclitaxel/bevacizumab/emactuzumab and after pre-infusion every 4 weeks for the patient safety lead-in (Part 1), and randomized therapy (Part 2B). In Part 2, we will seek to obtain 2 biopsies, one pre-treatment tissue biopsy prior to initiation of Part 2A and one pre-randomization tissue biopsy prior to initiation of Part 2B. These biopsied tissues will be used for monitoring dynamic changes in adapted macrophages (with phenotype of M2-like: VEGFR1-3+, CD markers (e.g. +CD68, CD163+), CSF1/CSF1R+ and MHCII^{low}), and hypoxia markers as well as CD4/CD8, NK, and T-reg. If a third biopsy is obtained (following progression) we will run a third set of tissue biomarkers; biopsy at progression is optional. In addition, we will also evaluate other molecular pathways (e.g., epigenetic modifications.
- To assess tumor alterations by serial non-invasive imaging macrophage-specific imaging, ADC (Apparent Diffusion Coefficient) for cellularity, and DCE (Dynamic Contrast Enhanced) for vasculature.

3. STUDY DESIGN

3.1 Overview of study design

This trial consists of 2 Parts:

3.1.1 Part 1 (Safety Lead-in):

Safety assessment in 9 patients of paclitaxel plus bevacizumab plus emactuzumab. To ensure patient safety, the first three patients will be enrolled staggered with one week between enrollments of each patient. All three patients must complete one cycle of triplet therapy prior to enrollment of any additional patients on Part 1 of the study. If no dose-limiting toxicities are observed, the remaining six patients may be enrolled simultaneously. If dose-limiting toxicities are observed at any time, refer to section 8.1.1 of the protocol for patient enrollment requirements. Doses to be used in this cohort will mimic the starting doses in Part 2B outlined in the next section. Specifically:

- Paclitaxel 80 mg/m^2 as a 1-hour i.v. infusion on days 1, 8, 15 and 22 q4w
- Bevacizumab 10 mg/kg i.v. d1,15
- Emactuzumab 1000 mg i.v. d1,15

Emactuzumab dose was chosen from the phase I dose escalation and confirmed in the phase I combination trial with paclitaxel. Emactuzumab should be administered before bevacizumab and then paclitaxel at the first cycle and throughout subsequent cycles.

For bevacizumab and paclitaxel, pre-medication should be implemented according to local practices. For emactuzumab, premedication may be administered, if needed, starting at Cycle 2 and at the discretion of the investigator.

Patients will be evaluated for tolerance of the triplet through 4 weeks of therapy. While a dose modification will be provided to account for toxicity, the non-overlapping adverse events seen in the paclitaxel plus emactuzumab phase I provide some confidence this triplet will be well tolerated as the doublet of paclitaxel plus bevacizumab

3.1.2 Part 2 (Induction/Randomization):

3.1.2.1 ***Part 2A (see Schema):***

Induction: all enrolees will receive paclitaxel plus bevacizumab for 2 cycles (8 weeks) and undergo evaluation for response

3.1.2.2 ***Part 2B (see Schema):***

Randomized phase II. Patients with stable disease will be randomized 1:1 to continued paclitaxel plus bevacizumab (Arm 1) or paclitaxel plus bevacizumab plus emactuzumab (Arm 2).
Arm 1 (Paclitaxel plus bevacizumab):
Eligible patients will receive:

- Paclitaxel 80 mg/m^2 as a 1-hour i.v. infusion on days 1, 8, 15 and 22 q4w.
- Bevacizumab 10 mg/kg i.v. on days 1 and15

These doses were chosen from the AURELIA trial which shares identical eligibility to the current trial and is the FDA approved doses for this chemotherapy backbone.
Pre-medication should be implemented according to local practices.
Upon disease progression patients in Arm 1 will receive standard of care.

Arm 2 (Paclitaxel plus bevacizumab plus emactuzumab):

- Arm 1 therapy and schedule will be used plus Emactuzumab 1000 mg i.v. on days 1 and 15 over 90 minutes

Emactuzumab should be administered before bevacizumab and then paclitaxel at the first cycle and throughout subsequent cycles. For bevacizumab and paclitaxel, pre-medication should be implemented according to local practices. For emactuzumab, premedication may be administered starting at Cycle 2, and at the discretion of the investigator.
In case paclitaxel is discontinued before diagnosis of progressive disease, patients should continue to receive emactuzumab at 1000 mg i.v. **d1,15** and bevacizumab 10 mg/kg i.v. **d1,15.**
After disease progression, study therapy should be discontinued permanently and patients will receive standard of care treatment.

3.1.3 Rationale for study design:

The trial will take place in two sequential Parts.

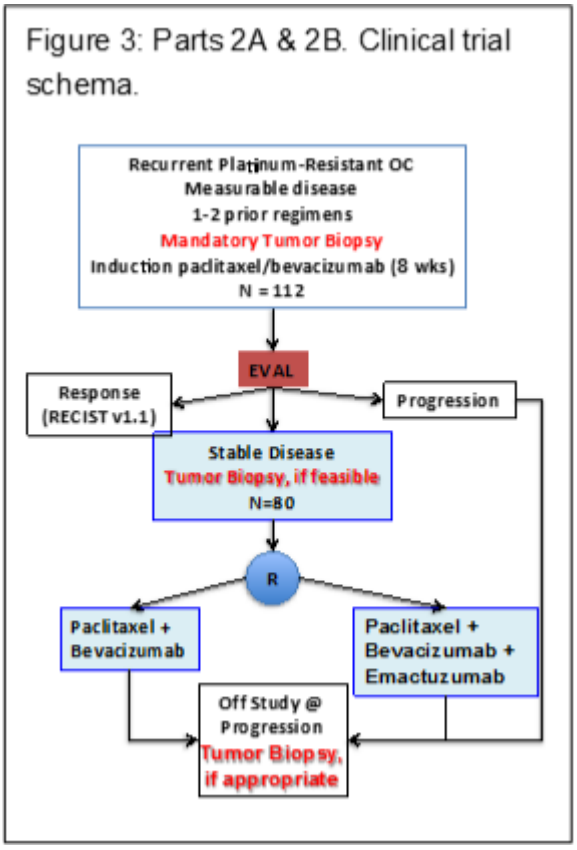
3.1.3.1 **Part 1 (safety lead-in):**

Although paclitaxel and bevacizumab have been extensively studied in AURELIA and other clinical trials, and paclitaxel and emactuzumab has been studied in a phase I trial upon which the phase II dose of emactuzumab was established, the triplet of paclitaxel, bevacizumab and emactuzumab has not been studied. There appear to be no drug-drug interaction or overlapping adverse events. The Part 1 safety lead-in will consist of 9 evaluable patients (receiving 1 cycle of triplet therapy). PD blood will be collected pre-infusion for translational analysis.Once patient 9 clears the toxicity window (1 cycle of triplet therapy), the trial will move to Parts 2A & 2B.

3.1.3.2 Parts 2A and 2B (induction/discontinuation randomized phase II):

The Figure 3 outlines the trial schema. The primary focus of the trial is to assess whether emactuzumab can overcome induced events in the tumor microenvironment limiting efficacy from paclitaxel plus bevacizumab. As outlined below, chemotherapy and bevacizumab can impact the profile of infiltrating mononuclear cells and macrophages to overcome anti-VEGF targeting. The trial design was chosen to optimize and identify that cohort of women neither primarily progressing on paclitaxel/bevacizumab (primary refractory) nor demonstrating rapid response. Part 2A patients will undergo tissue biopsy to establish primary and provide material for pharmacodynamic testing and then initiate treatment on paclitaxel plus bevacizumab therapy in the doses and schedule outlined in the package insert for this FDA-approved combination. Only one assessment cycle (8 weeks = 2 courses) will be used to evaluate those with rapid progression or response. Those with stable disease will enter Part 2B, and will undergo a follow-up biopsy and then randomization to either continued therapy (standard of care) or triplet therapy adding emactuzumab. The primary efficacy endpoint (progression-free survival) will compare the randomized cohort. Paired tissue sampling will be interrogated for tumor microenvironment cellular perturbations.

Figure 3: Parts 2A & 2B. Clinical trial schema.



3.1.4 Rationale for dose selection

In the AURELIA study, paclitaxel 80 mg/m^2 as a 1-hour i.v. infusion was administered on days 1, 8, 15 and 22 along with bevacizumab 10 mg/kg days 1 and 15 on a 28-day cycle. This schedule will be used in the current study for both the induction phase (Part 2A: all patients) and randomization phase (Part 2B: control population following randomization).
Emactuzumab dosing was chosen from the phase I paclitaxel plus emactuzumab trial identifying 1000 mg flat dose administered every 2 weeks to be optimal with weekly paclitaxel at this schedule.
The combination of weekly paclitaxel plus bevacizumab plus emactuzumab will be administered during Part 1 (safety lead in) as well as in Part 2 (randomized experimental group)

3.1.5 Rationale for Tumor biopsy

TAM infiltration and differentiation is dependent on the respective tumor micro-milieu in primary and metastatic lesions. Furthermore the respective immune status and pre-treatment of the patient might influence the patient's tumor microenvironment. Therefore all patients entering Part 2A will undergo a mandatory pre-treatment biopsy to define the TAM infiltration and CSF-1R expression levels at baseline but will not be used to determine patient eligibility for the trial.

Archival tumor tissue cannot substitute for the fresh biopsies as macrophage infiltration and differentiation is micro-milieu dependent. The tumor micro-milieu may be variable in the primary tumor due to pre-treatment of the patient and as well be altered in metastatic lesions. To better understand this potential heterogeneity,

collection of archival tissue will also be done. Patients enrolling onto Part 2B will undergo a second biopsy to evaluate induced microenvironment alterations in cellular populations that represent incomplete clinical response to induction paclitaxel plus bevacizumab. Patients demonstrating primary progression after Part 2A will be approached for an off-treatment biopsy to understand alterations representing this poor clinical response.

3.2 End of study

End of study is defined as the date of the last visit of the last patient. The primary analysis will be performed once at least 50 events of disease progression or death have been observed in those randomized, or at the end of study which ever occurs first. Patients are anticipated to be followed for a minimum of 6 months for PFS. Follow-up for survival will continue for up to 5 years for each patient; patients with progression in Part 2A will not be followed after the 30 Day Follow Up-Visit. Patients who progress in Parts 1 and 2B will be followed for overall survival, see Section 8.2.3. Please refer to schedule of events designated in Tables 1 - 3. The trial may be prematurely terminated if recommended by the DSMB (refer to section 9.4)

3.3 Number of patients

It is expected that 121 patients will be recruited into the trial; 9 in Part 1 and 112 in Part 2

3.4 Participating Sites

This will be initiated at M.D. Anderson Cancer Center during Part 1 and then open in Part 2 at the following Houston Area Locations (HALs): M.D. Anderson in Sugar Land, Katy, Woodlands, Bay Area, and Woman's Hospital of Texas. Part 2 will also open in the Cancer Network Partner M.D. Anderson Cooper Hospital, as well as two outside institutions, the University of Texas Southwestern Medical Center and the University of Oklahoma for Part 2A & 2B.

3.5 Randomization and stratification

Eligible patients will be allocated in Part 2B in a randomized fashion (1:1 ratio) to receive paclitaxel plus bevacizumab (Arm 1) or paclitaxel plus bevacizumab plus emactuzumab (Arm 2). To ensure the equal distribution of prognostic factor in the two study arms, patients will be stratified according to the following parameters

- Platinum-free interval (TFI) < 3 months vs 3 to 6 months.

Note: PFI is assessed according to the last platinum-based regimen administered (defining the patient as "platinum-resistant" as per inclusion number 4). PFI is calculated from the date of that last platinum treatment to the date of the subsequent disease progression.

A Patient Enrollment and Identification Code List must be maintained by the investigator.

All patients must commence treatment within 7 days following randomization; otherwise, the screening assessments will need to be repeated. Please note that subject to the availability of study medication at site, the first dose of study treatment (Cycle 1 Day 1) may also be the day of randomization.

4. STUDY POPULATION

4.1 Overview

The REDIRECT study will enroll adult patients with epithelial ovarian cancer (EOC), fallopian tube carcinoma (FTC) or primary peritoneal carcinomas (PPC) who have undergone an appropriate attempt at, or completed primary platinum resistant therapy, as deemed by the investigator, for their initial disease. Patients will be considered eligible for enrollment in this trial if they fulfil the inclusion criteria and none of the exclusion criteria as defined below.

4.2 Inclusion criteria

1. Signed informed consent obtained prior to initiation of any study-specific procedures and treatment as confirmation of the patient's awareness and willingness to comply with the study requirements (inclusive of 2 biopsies, one at baseline and if they qualify, one pre-randomization for part 2B).
2. Women 18 years of age or older.
3. Histologically confirmed and documented disease to include: adenocarcinoma NOS, clear cell adenocarcinoma, endometrioid adenocarcinoma, malignant Brenner's tumor, mixed epithelial carcinoma, mucinous adenocarcinoma, serous adenocarcinoma, transitional cell carcinoma, and undifferentiated carcinoma.
4. Patients must have undergone an appropriate attempt at, or completed, primary platinum based therapy, as deemed by the investigator, for their initial disease. Patient must have recurrent disease documented by imaging or elevated CA-125 within 6 months of last dose of platinum treatment.
5. Patients must have disease that is measurable according to RECIST 1.1. If no measureable disease is present, patients should have assessable disease such as pleural effusion, ascites, with GCIG CA-125 criteria and require chemotherapy treatment.
   Part 1: Patients must have have one or more measurable target lesion or assessable disease such as pleural effusion, ascites with GCIC CA-125 criteria.Patients with non-measureable disease but evaluable solid tumors may be deemed eligibile contingent upon PI review.

Part 2: Patients must have two or more measurable target lesions or assessable disease such as pleural effusion, ascites with GCIC CA-125 criteria. Patients with non-measureable disease but evaluable solid tumors may be deemed eligibile contingent upon PI review.

   a. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each "target" lesion must be ≥20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥10 mm when measured by spiral CT.

6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Newly obtained core or excisional biopsy of a tumor lesion for Part 2A and if they qualify, one pre-randomization biopsy for part 2B.
8. Adequate organ function as determined by the following laboratory values:
   a. Absolute neutrophil count ≥1,500 /mcL.
   b. Platelets ≥100,000 / mcL.
   c. Hemoglobin ≥9 g/dL or ≥5.6 mmol/L.
   d. Creatinine Clearance ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN.
   e. Total Bilirubin ≤ 1.5 X ULN
      OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN.
   f. AST (SGOT) and ALT (SGPT) ≤ 2.5 X ULN
      OR ≤ 5 X ULN for subjects with liver metastases.
   g. INR/PT ≤1.5 X ULN (unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants).
   h. PTT ≤1.5 X ULN (unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.
9. Life expectancy of ≥12 weeks.

4.3 Exclusion criteria

Cancer-related

1. Patients who have disease progression prior to an appropriate attempt at, or completed primary platinum based therapy, as deemed by the investigator, for their initial disease, including patients demonstrating disease progression after interval cytoreduction.
2. Non-epithelial, including malignant mixed Müllerian tumors.
3. Ovarian tumors with low malignant potential (i.e. borderline tumors).
4. For Part 2 patients only: History of other clinically active malignancy within 5 years of enrollment, except for tumors with a negligible risk for metastasis or death, such as adequately controlled basal-cell carcinoma or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix or breast, or early stage endometrial cancer (stage IA/B, Grade 1 or 2, endometrioid histology).

Prior, current or planned treatment:

5. Previous treatment with >2 anticancer chemotherapy regimens for ovarian cancer.
6. Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment, with the following exceptions:
   - Hormone-replacement therapy or oral contraceptives.
   - Tyrosine kinase inhibitors (TKIs) that have been discontinued > 7 days prior to Cycle 1, Day 1; screening scans must be obtained after discontinuation of prior TKIs.
7. Any prior radiotherapy to the pelvis or abdomen.
8. Surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury within 28 days prior to study enrollment, or anticipation of need for major surgical procedure during the course of the study. Minor surgical procedures including placement of a vascular access device, within 2 days of the first study treatment.
9. Previous exposure to murine CA-125 antibody (only applicable to those patients with non-measurable disease by RECIST).
10. Current or recent (within 10 days prior to the first study drug dose) chronic daily treatment with aspirin (>325 mg/day).
11. Current or recent treatment with another investigational drug within 30 days of first study treatment dosing or earlier participation in this study.
12. **Treatment with systemic immunosuppressive medications** (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents within 2 weeks prior to Cycle 1, Day 1. Patients who have received acute and/or low-dose systemic immunosuppressant medications or anticipation of need for major surgery, a one-time dose of dexamethasone for nausea or chronic use of ≤ 10 mg/day of prednisone or dose-equivalent corticosteroid) may be enrolled in the study after discussion with and approval by the IND Office Medical Monitor. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed. Prior corticosteroids as anti-cancer therapy within a minimum of 14 days of first receipt of study drug.
13. **Received therapeutic oral or IV antibiotics** within 2 weeks prior to Cycle 1, Day 1. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
14. Patients with urine dipstick for proteinuria >2+. Patients with ≥2+ proteinuria on baseline dipstick analysis should undergo a 24-hour urine collection and must demonstrate ≤1 g of protein in the 24-hour urine. Alternatively, proteinuria testing can be performed according to local standards.

Prior or concomitant conditions or procedures:

15. Patients with known auto-immune disease.
16. Patients with known history of HIV, HBV and HCV infection.
17. Patient has received an organ transplant.
18. Patient has a history of hematological malignancy within the last 5 years prior to study entry, prior allogeneic bone marrow transplantation or prior solid organ transplantation.
19. History of or active autoimmune disease including, but not limited to, systemic lupus erythematous, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, and vasculitis or glomerulonephritis. Patients with autoimmune thyroid disease on a stable thyroid replacement regimen; controlled vitiligo, eczema, psoriasis, or seborrhoic dermatitis with only dermatologic manifestations; or controlled Type I diabetes on a stable insulin regimen may be eligible for the study with approval by the Medical Monitor.
20. History or evidence upon physical / neurological examination of CNS disease unrelated to cancer, unless adequately treated with standard medical therapy (e.g. uncontrolled seizures).
21. Symptomatic CNS metastasis.
22. Pre-existing peripheral neuropathy ≥ CTC grade 2 for those patients who received prior paclitaxel.
23. Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to screening.
24. Increased corrected QT (QTc) interval (QTc > 470 ms), patients with baseline resting bradycardia < 45 bpm, or baseline resting tachycardia > 100 bpm.
25. Family history of long QT syndrome or other risk factors for torsades de pointes, and/or the use of concomitant medications that prolong the QT/QTc interval.
26. Signs or symptoms of serious active infection requiring oral or i.v. antibiotics within 2 weeks prior to Cycle 1 Day 1 and/or hospitalization at study entry including, but not limited to, hospitalization for complications of infection, bacteremia, active tuberculosis or severe pneumonia.
27. Pregnant or lactating females. Serum pregnancy test to be assessed within 7 days prior to study treatment start.
28. For women who are not postmenopausal (<12 months of non therapy-induced amenorrhea, with no identified cause other than menopause) and have not undergone surgical sterilization (removal of ovaries and/or uterus): agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate non hormonal methods of contraception, including at least one method with a failure rate of <1% per year, during the treatment period and for at least 4 months after the last dose of study drug. Examples of non-hormonal contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
29. History or evidence of thrombotic or hemorrhagic disorders; including cerebrovascular accident (CVA) / stroke or transient ischemic attack (TIA) or sub-arachnoid hemorrhage within ≤6 months prior to the first study treatment.
30. Uncontrolled hypertension (sustained systolic >150 mmHg and/or diastolic >100 mmHg despite antihypertensive therapy) or clinically significant (i.e. active) cardiovascular disease, including:
    - myocardial infarction or unstable angina within ≤6 months prior to the first study treatment.

- New York Heart Association (NYHA) grade II or greater congestive heart failure (CHF).
- serious cardiac arrhythmia requiring medication (with the exception of atrial fibrillation or paroxysmal supraventricular tachycardia).
- Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior of study enrollment.
- Prior history of hypertensive crisis or hypertensive encephalopathy.

31. History of bowel obstruction, including sub-occlusive disease, related to the underlying disease and history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess. Evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction.
32. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).
33. History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month of study enrollment for any tumor type.
34. Non-healing wound, ulcer or bone fracture.
35. Known hypersensitivity to any of the study drugs or excipients.
36. Evidence of any other medical conditions (such as psychiatric illness, peptic ulcer, etc.), physical examination or laboratory findings that may interfere with the planned treatment, affect patient compliance or place the patient at high risk from treatment-related complications.

4.4 Concomitant medication and treatment

All concomitant medications must be recorded in the eCRF, Prometheus. Throughout the study, investigators are permitted to use their clinical judgement when prescribing concomitant medications and treatments for trial patients. Local prescribing information and institutional guidelines should be followed as applicable. In all cases, concomitant medications and treatments should only be used with the intention of either maintaining existing medical conditions, or controlling cancer-related symptoms or treatment-related complications. Caution should be exercised when using treatments that could potentially interfere with any of the study medications or the interpretation of the study results. For specific information, please refer to the paclitaxel and bevacizumab product package inserts for prescribing information and the emactuzumab Investigator's Brochure.

For example, prophylactic pre-medication for prevention of treatment-related side effects like nausea or hypersensitivity reactions has to be distinguished from new supportive medication used to maintain existing medical conditions (e.g. prophylactic heparin for prior DVT), to control cancer-related symptoms (e.g. pain killers) or for treatment-related complications (e.g. platelet transfusion in case of severe thrombocytopenia or G-CSF support in case of severe neutropenia). Prophylactic pre-medication does not need to be documented whereas supportive medication should be documented within eCRF.

4.4.1 Permitted Therapy

Patients are allowed full supportive care therapies concomitantly during the study.

No other anti-cancer therapy will be permitted while the patients are receiving study therapy.

After Cycle 2, palliative radiation is permitted for irradiating small areas of painful metastases that cannot be managed adequately by systemic or local analgesics. Before initiation of palliative radiation therapy, a bone metastatic work up should be repeated to rule out disease progression.

Any disease progression that requires other forms of specific anti-tumor therapy will be cause for early discontinuation of study treatment.

4.4.2 Prohibited Therapy

Patients should be treated for all concomitant medical conditions and adverse events according to accepted standards of medical care at the discretion of the investigator. The following treatments are not permitted during the study:

- Any other investigational therapy
- Cytotoxic chemotherapy agents
- Radiotherapy (as per inclusion criteria). After Cycle 2, certain forms of radiotherapy may be considered for pain palliation (e.g., treatment of known bony metastases).
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. Systemic corticosteroids, TNF-α inhibitors, mycophenolate, and other immune suppressants may be administered for the treatment of immune-related toxicities at the discretion of the treating physician after consultation with the Medical Monitor.
- Other systemic anti-neoplastic agents and targeted therapies

If any anti-neoplastic or investigational therapies listed above are needed, the patient will be considered to have evidence of progressive neoplastic disease and have experienced treatment failure with study treatment and should be withdrawn from study treatment.

Patients who experience a mixed response that requires local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, and/or radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the IND Medical Monitor.

4.5 Criteria for premature withdrawal

Patients have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, AEs, treatment failure after a prescribed procedure, protocol violation, cures, administrative, or other reasons. Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an AE, the principal specific event will be recorded on the eCRF.

In case the patient decides to prematurely discontinue study treatment ("refuses treatment"), the patient should be asked if they can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the eCRF.

4.6 Replacement policy

An excessive rate of patient withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. For additional information, please refer to Section 9.4. Patients who prematurely withdraw from the study will not be replaced. The study sample size has been adjusted to accommodate an estimated 15% drop out rate for progressive disease/toxicity. Only patients amenable

to continued therapy after induction (8 weeks) in whom disease has neither progressed nor responded (RECIST criteria) will be randomized.

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Please refer to Tables 1 - 3 detailing the schedule of assessments for Part 1 and Part 2 of the study.

5.1 Screening examination and eligibility screening form

All patients must provide written informed consent before any study-specific assessments or procedures are performed. Patients who fulfil all the inclusion and none of the exclusion criteria will be accepted into the study.

A screening physical examination should be performed within 7 days prior to the first day of treatment. Please refer to schedule of events designated in Tables 1 and 2.

A study entrance note documenting the investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator and placed in the patient's electronic medical record

A screen failure log will be maintained by the investigator.

5.2 Procedures for enrollment of eligible patients

Once a patient has fulfilled the entry criteria, they will be assigned a unique patient identification number when enrolled into the study. A patient enrollment list will be maintained by the investigator.

5.3 Clinical assessments and procedures

5.3.1 Tumor response criteria

Tumor response will be evaluated according to RECIST, CA-125 (http://www.gcig.igcs.org/CA-125.html) and clinical criteria (see **Appendix 1**).

In this study, disease progression is defined as per RECIST guidelines on radiological, clinical or symptomatic progression. CA-125 elevation alone is not defined as disease progression unless accompanied by clear radiological, clinical or symptomatic progression. **Patients on treatment who are well but have rising CA-125 levels should continue protocol treatment until RECIST defined radiological, clinical or symptomatic progression of disease.**

5.3.2 Tumor imaging

Tumor assessments for response and progression require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast media. Throughout the study, the same assessment technique must be used. Ultrasound scanning is not an acceptable substitute for CT scanning.

Evaluation of response by RECIST criteria should be performed at baseline then every 8 weeks. A second CT scan performed not earlier than 4 weeks after the criteria for response are first met will confirm responses. Please refer to schedule of events designated in Tables 1-3.

5.3.3 CA-125

Serum CA-125 will be assessed per standard of care. Please refer to schedule of events designated in Tables 1-3. The same laboratory throughout the study period should assess CA-125 and centers are required to submit the normal ranges for CA-125 for the laboratories they use. CA-125 measurement is not required following disease progression. Please refer to http://www.gcig.igcs.org/CA-125.html.

5.3.4 Scheduling of tumor assessments

Baseline assessments require CT scans of the pelvis and abdomen and (by X-ray or preferably by CT-scan) of the chest. MRI scans can be used for patients who are allergic to radiographic contrast media. Patients will be assessed for disease response or progression throughout the study according to RECISTusing the same imaging modality as used during screening. If the patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present. Please refer to schedule of events designated in Tables 1-3.

5.3.5 Physical examination and measurement of vital signs

Patients will undergo a complete physical examination (including observable tumor measurements), weight and measurement of vital signs (blood pressure) per timepoints designated in Tables 1-3.

5.3.6 Performance status

PS will be measured using the ECOG performance status scale (see **Appendix 2**). It is recommended, where possible, that a patient's PS be assessed by the same person throughout the study. Please refer to schedule of events designated in Tables 1-3.

5.3.7 Clinical safety assessments

The NCI CTC-AE version 4.03 will be used to evaluate the clinical safety of the treatment in this study. Patients will be assessed for AEs at starting at the time of signed informed consent and throughout the study. Please refer to schedule of events designated in Tables 1-3.

5.4 Laboratory assessments

Laboratory safety assessments will be performed per the schedules of events designated in Tables 1-3. All testing will be conducted locally. Outside labs will be allowable, however the PI/treating physician must review, determine clinical significance, and sign and date these reports. The total volume of blood taken will be approximately 15 ml per visit.

5.4.1 Efficacy laboratory assessments

As described in Section 5.3.1.2, CA-125 will be monitored over the course of the study in order to assess responses.

5.4.2 Safety laboratory assessments

Laboratory tests should be performed as per local standard of care in order to monitor patient safety. However, as a guide, this could include the following assessments:

- Hematology (hemoglobin, platelet count, full white blood count, including differential)
- Biochemistry (sodium, potassium, calcium, blood urea nitrogen (BUN), uric acid, total protein (or albumin only), alkaline phosphatase, creatinine kinase, AST/SGOT, ALT/SGPT, GGT, LDH, total bilirubin, blood glucose, creatinine)
- Coagulation tests (INR and aPTT)
- Urinalysis by dipstick: Proteinuria testing can be performed according to local standards.
- Pregnancy test in women of child-bearing potential: Serum pregnancy test within 7 days prior to the first study treatment or within 14 days with a confirmatory urine pregnancy test within 7 days prior to the first study treatment.

- ECGs will be performed at baseline and repeated during the study as clinically indicated.
- Note: Only AEs grade 2–5 will need to be recorded in the eCRF.

5.5 Pharmacodynamic and Biomarker Assessments

To fully assess the utility of surrogate biomarkers and the anti-tumor response to therapy with the combination treatment of bevacizumab and emactuzumab, we will draw 20 ml blood for plasma markers (VEGF, VEGFR, IL6, IL8, FGF, PDGFAA, CSF1, and IL34) and other chemokines identified by secretome proteomics) and potential exosomal markers (M2-like markers VEGFR1-3, CD11b +CD68, CD11b+CD14/CD15/CD33, CD11b+CD11c, MHCII), prior to initiation of paclitaxel/bevacizumab/emactuzumab and at time points noted in Table 4 for the patient safety lead-in (Part 1), and induction and randomized therapy (Part 2A & 2B). All PD blood draws are mandatory. In Part 2A, there will be one mandatory pre-treatment biopsy and one optional biopsy at progression. In the Part 2B, we will seek to obtain 2 biopsies, one at pre-treatment tissue biopsy prior to initiation of bevacizumab (Part 2A portion) and one pre-randomization tissue biopsy following 4 weeks from last dose of bevacizumab (at pre-infusion of emactuzumab), and optionally at progression. These biopsied tissues will be used for monitoring dynamic changes in adapted macrophages (with phenotype of M2-like: VEGFR1-3+, CD markers (e.g. +CD68, CD163+), CSF1/CSF1R+ and MHCII^{low}), and hypoxia markers as well as CD4/CD8, NK, and T-reg. Please refer to schedule of events designated in Tables 1-4.

In addition to IHC assays, DNA/RNA next generation sequencing may be performed for genotype-protein expression. Internal/External Sequencing may be done here at MDACC, in one of the Core labs such as the Cancer Genomics Lab, but in some cases samples may be sent to outside collaborators for sequencing and/or analysis such as Broad Institute. Any sharing or sequencing of samples performed by Broad or any other external collaborator will be conducted under specific contract or Material Transfer Agreement (MTA). We will protect participant's privacy by coding samples and keeping the master list of identifiers accessible to only key project staff. Data will be kept on secure computers and samples will be kept in freezers in locked laboratories and buildings. Additionally in some other cases, samples may be provided from outside collaborators or institutions for discovery and research purposes. In such cases, the samples should be obtained under IRB-approved protocols at these outside collaborators and institutions to allow them for participation in this protocol and under a specific grant/ contract or Material Transfer Agreement (MTA) with MDACC.

5.5.1 Handling of Specimens

Biopsies: Biopsies will be obtained directly or by image guided techiniques in study Parts 2A & 2B. A simple biopsy will be obtained for each time point when possible. Ideally, 5 pass needle samples will be obtained using a 22 gauge or larger needle at the discretion of the interventional radiologist for each time point in order to obtain adequate tissue. Ideally a 16 gauge needle will be utilized. A portion of each biopsy sample (4 cores) will be snap-frozen immediately, then the remainder of the biopsy sample (1 core) will be collected into a 2mL cryotube for further analysis. PD blood & tissue samples will be shipped to M.D. Anderson Cancer Center and stored in the laboratory of Dr. Anil Sood. Shipping, collection, and processing instructions are found in Appendix E (Lab Manual).

Blood Plasma: 10 ml of venous blood plasma is collected in a lavender top (EDTA) Vacutainer tube.

Blood Serum: 10 ml of venous blood is collected in a red top (serum) Vacutainer tube.

5.5.2 Storage of Specimens

PD blood and tissue samples will be stored and analyzed in the laboratory of Dr. Anil Sood, M.D. at MD Anderson Cancer Center.

Contacting Dr. Anil Sood's laboratory for analyses:

Attn: Anil Sood and Nicholas Jennings
Department of Gynecologic Oncology and Reproductive Medicine
1881 East Road
3SCR3.4640
Houston, TX 77054

5.5.3 Labeling of Specimens

Each specimen will be labeled with a study bank ID number, a specimen code, and the collection date. The specimen code will be assigned sequentially and FFPE will be used for the FFPE archived tissue. Please reference Appendix E (Lab Manual) for detailed instructions.

5.6 End of Treatment Visit

An end of treatment evaluation should be performed within 4 weeks of the last dose of study drug for Part 1 and both arms of Part 2 of the study. Please refer to schedule of events designated in Tables 1-3.

5.7 Safety follow-up

Patients enrolled in the trial will remain on treatment until disease progression, unacceptable toxicities or patient request for withdrawal.

5.7.1 30-Days Safety Follow-Up

All patients must undergo a 30 Day Safety Follow-Up assessment 30 days +/- 5 days after the last dose of therapy. Please refer to schedule of events designated in Tables 1-3.

5.8 Survival follow-up

Patients with complete response will be followed for up to 5 years; patients with progression in Part 2A will not be followed after the 30 Day Follow Up-Visit. Patients who progress in Parts 1 and 2B will be followed for overall survival, see Section 8.2.3. Please refer to schedule of events designated in Tables 1 - 3.

5.9 Study exit

Once the patient has completed all study visits and exited the study, they will be managed by their physician in accordance with local standards of care.

6. INVESTIGATIONAL MEDICINAL PRODUCTS

In this study, emactuzumab is considered to be the 'investigational study drug'. Paclitaxel and bevacizumab are considered to be standard-of-care 'non-investigational combination drugs'. Collectively, they will be known as the 'study treatments'.

6.1 Dose and schedule of study treatments

This trial consists of 2 Parts:
Part 1: safety assessment in 9 patients of paclitaxel plus bevacizumab plus emactuzumab. Doses to be used in this cohort will mimic the starting doses in Part 2B outlined in the next section. Specifically:

- Paclitaxel 80 mg/m^2 as a 1-hour i.v. infusion on days 1, 8, 15 and 22 q4w
- Bevacizumab 10 mg/kg i.v. on days 1 and 15
- Emactuzumab 1000 mg i.v. on days 1 and 15

Emactuzumab infusion should be given first.
Patients will be evaluated for tolerance of the triplet through 4 weeks of therapy. While a dose modification will be provided to account for toxicity, the non-overlapping adverse events seen in the paclitaxel plus emactuzumab phase I provide some confidence this triplet will be well tolerated as the doublet of paclitaxel plus bevacizumab. Patients in this Part will stay on therapy until progression, intolerable toxicity or confirmed RECIST complete response.

Part 2A (see Study Schema, Section 3.1): Induction: all enrollees will receive paclitaxel plus bevacizumab for 2 cycles (8 weeks) and undergo evaluation for response (RECIST)

- Paclitaxel 80 mg/m^2 as a 1-hour i.v. infusion on days 1, 8, 15 and 22 q4w.
- Bevacizumab 10 mg/kg i.v. on days 1 and 15

Part 2B (see Study Schema, Section 3.1): Randomized phase II. Patients with stable disease will be randomized 1:1 to continued paclitaxel plus bevacizumab (Arm 1) or paclitaxel plus bevacizumab plus emactuzumab (Arm 2).
Arm 1 (Paclitaxel plus bevacizumab):
Eligible patients will receive:

- Paclitaxel 80 mg/m^2 as a 1-hour i.v. infusion on days 1, 8, 15 and 22 q4w.
- Bevacizumab 10 mg/kg i.v. d1,15

These doses were chosen from the AURELIA trial, which shares identical eligibility to the current trial and is the FDA approved doses for this chemotherapy backbone.
Pre-medication should be implemented according to local practices. For premedication for emactuzumab please see section 4.4.1 and 6.6.3
Upon disease progression patients in Arm 1 will receive:

- Standard of care.

Arm 2 (Paclitaxel plus bevacizumab plus emactuzumab):
Eligible patients will receive:

- Arm 1 therapy and schedule will be used plus **Emactuzumab 1000 mg i.v. q2w over 90 minutes**
- Emactuzumab dose was chosen from the phase I dose escalation and confirmed in the phase I combination trial with paclitaxel. Emactuzumab should be administered before bevacizumab and then paclitaxel at the first and all subsequent cycles

In case chemotherapy is discontinued before diagnosis of progressive disease, patients should continue to receive emactuzumab at 1000 mg i.v. q 2 wks and bevacizumab 10 mg/kg i.v. q2w
After disease progression, patients will receive standard of care treatment.
Upon clear evidence of disease progression, study therapy should be discontinued permanently.

6.2 Dose modifications and delays

In general, a dosing delay of up to 3 weeks is allowed in case of grade 3 or greater non-hematologic toxicity including laboratory abnormalities or any hematologic toxicity including Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with bleeding, Grade 4 neutropenia persisting > seven days, febrile neutropenia, or Grade 4 anemia to reduce toxicity to baseline or grade 0-1. Dose delays greater than 3 weeks will lead to the withdrawal of the patient from the treatment.

Patients experiencing asymptomatic elevation of liver enzymes may continue on study however, close monitoring of liver function parameters is required. Refer to section 6.3.9.2.2 for management guidelines for hepatic events. Dose levels will be adjusted only for paclitaxel in Section 6.5.1. No dose modifications will be made for bevacizumab or emactuzumab, please refer to Sections 6.3.9 and 6.4.3 for dose holding rules. No dose re-escalations are planned following dose reduction for toxicity for any of the study treatments.

6.3 Emactuzumab: Preparation and Administration of

6.3.1 Formulation, Packaging and Labeling of Emactuzumab

Emactuzumab is provided as a sterile, preservative-free liquid, in single dose 10 mL glass vials buffered histidine solution (pH 6.0) containing, trehalose dihydrate, polysorbate 20 and water for injection. The approximate concentration of emactuzumab in the vials is 25 mg/mL. The study drug must be stored according to the details on the product label and in the container provided. Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, and temperature conditions, confirm receipt and report any deviations or product complaints upon discovery to the monitor.

6.3.2 Preparation of Emactuzumab

The infusion volume is 250 mL. After withdrawal of an appropriate volume based on the patient's dose level, emactuzumab should be further diluted in 0.9% (w/v) sodium chloride solution prior to administration as an iv infusion at room temperature (18 °C - 24 °C). Before adding the appropriate volume of emactuzumab to the 0.9% (w/v) sodium chloride infusion bag the respective volume of 0.9% (w/v) sodium chloride solution is withdrawn from the infusion bag and discarded.

The final emactuzumab drug solution will be administered intravenously using an inline filter (0.2 µm) and should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 to 8°C or 4 hours at ambient temperature (18^0C to 24^0C). Potential drug products should be inspected visually for particulates prior to administration. Partially used vials MUST NOT be re-used. DO NOT SHAKE AND DO NOT FREEZE VIAL CONTENTS.

Chemical and physical in-use stability for emactuzumab dilutions in 0.9% sodium chloride have been demonstrated for 24 hours at 2 to 8°C and/or at ambient temperature (18 °C - 24 °C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibilities of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Details on the recommended product contact surfaces for inline filter, administration set and infusion bag, as well as the tested emactuzumab concentrations and infusion speed are described separately in the investigator binder provided to the clinical centers.

Details regarding preparation of emactuzumab for infusion will be provided in the Drug Procedures Manual, which will be provided to sites prior to the start of the study.

6.3.3 Premedication

Specific premedication for emactuzumab infusion is not necessary. No premedication will be allowed for the first dose of study treatment. Premedication is required for patients with a prior infusion reaction. Premedication may be administered starting at Cycle 2 at the discretion of the treating physician. A recommended treatment plan for premedication would be an anti H3, such as famotidine given at 25mg i.v.; Benadryl given at 25mg i.v.; and a steroid, such as dexamethasone given at 10mg i.v. or their equivalents. If hypersensitivity occurs despite premedication, the patient must be removed from study.

6.3.4 Administration of Emactuzumab (Parts 1 and 2B)

Emactuzumab will be administered as a flat (absolute) dose of 1000 mg as i.v. infusion over 90 mins. All patients will receive their assigned dose of emactuzumab. A central line is required prior to treatment.

During infusion, vital signs (including supine blood pressure, respiratory rate, pulse rate and temperature) have to be monitored pre-infusion, every 15 minutes until the end of infusion, and thereafter, every 30 minutes until the infusion line is removed. After the end of infusion, the i.v. line should remain in place for 2 hours. If no infusion-related symptoms occur after 2 hours, the infusion line may be removed. For subsequent infusions, the i.v. line should remain in place for 1 hour from the end of infusion and if no AEs occur after 1 hour, the infusion line may be removed. If an infusion reaction develops, the infusion should be temporarily slowed down or interrupted according to section 6.3.9.1.

For the management of infusion reaction and hypersensitivity reactions, see Section 6.3.9.1.

6.3.5 Rate of Infusion of Emactuzumab

Dose, date and time of the infusion commencement, date and time of end of infusion (EOI), interruption or adjustment in infusion rate, Arm, and the reason will be recorded for each patient. If infusion is interrupted, the date and time of stopping and resuming infusion will be recorded.

6.3.6 Assessment of Compliance

Accountability and patient compliance will be assessed, by maintaining adequate “drug dispensing” and return records.

Accurate records must be kept for each study drug. These records must contain the following information:

- documentation of drug shipments received from the sponsor (date received and quantity)
- disposition of unused study drug not dispensed to patient

A Drug Dispensing Log must be kept current and should contain the following information:

- the identification of the patient to whom the study medication was dispensed
- the date(s), quantity of the study medication dispensed to the patient

This inventory must be available for inspection. Copies of the Emactuzumab dispensing & inventory logs must be maintained by each site’s Investigational Pharmacy and made available upon request.

6.3.7 Destruction of Emactuzumab

Local or institutional regulations may require immediate destruction of used investigational product for safety reasons e.g., cytotoxicity. In these cases, it may be acceptable for investigational site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the drug supplier at study start up before destruction.

Written documentation of destruction must contain the following:

- Identity (batch numbers or patient numbers) of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of responsible person who discarded the investigational product in a hazardous container for destruction

Per the institutional site's policy, all empty or partially used containers of investigational agents are to be treated as hazardous substances with disposal occurring immediately after use into the chemotherapy waste-stream containers. MDACC Pharmacy will not retain or store used vials of investigational injectable or liquid oral medications for accountability purposes. Medications that expire will be held for 30 days from date of expiration for sponsor disposition. At the end of 30 days, any remaining expired drug will be destroyed per the Chemotherapy and Hazardous Substance Waste Stream Disposal Policy. Please refer to MD Anderson Investigational Pharmacy policy.

6.3.8 Reconciliation

MD Anderson agrees to conduct reconciliation for the product. Genentech and MD Anderson will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party.

If discrepancies are identified, the MD Anderson study team and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The MD Anderson study team shall receive reconciliation guidance documents within the 'Activation Package

6.3.9 Dose Modifications and Delays

Part 1: After the toxicity assessment period has been completed, a delay of Emactuzumab administration for up to 3 weeks will be acceptable. Dose reductions are not permitted in the toxicity assessment interval of the first cycle. Infusions/cycles will not be considered as missed but as delayed if a patient does not meet parameters for treatment. In case of a delay of an administration of more than 21 days for any reason, additional doses will not be administered and the patient will be withdrawn from all study treatment: Paclitaxel, Bevacizumab, and Emactuzumab. After the first cycle toxicity assessment period is complete

dose reductions for Emactuzumab will be allowed, refer to Table 7 for hepatic toxicities and Table 8 for Dermatological toxicities.

Patients may continue on treatment for Grade 3 or 4 laboratory parameters that may be elevated due to decreased clearance in the liver due to Kupffer cell depletion including CK, LDH and transaminases (ALT/AST), if not associated with clinical signs and symptoms (see section 6.3.9.2.2 for details on expected asymptomatic decreases in hepatic clearance). Close monitoring of liver function parameters (including Total Bilirubin, Creatinine Kinase, LDH, AST, ALT, Alkaline Phosphatase, Albumin, GGT, aPTT/INR) is required to ensure that the asymptomatic increases in LFTs due to Emactuzumab are not masking signs of true liver damage due to other reasons. If ALT/AST elevation is 3x ULN in combination with elevation in T Bili above 2.0x UNL, the patient has reached threshold for Hy's Law and all treatment will be permanently discontinued. Refer to Table 7 and section 6.3.9.2.2 for management guidelines for hepatic events.

	Initial	**First Dose Reduction**	**Second Dose Reduction**
Dose Level of Emactuzumab	**1000mg**	**670mg**	**500mg**

Part 2B: If treatment is delayed for any reason infusions/cycles will not be considered as missed but as delayed. If all treatment including Emactuzumab is held for more than 21 days due to toxicity patient may continue on Taxol and Bevacizumab if criteria for re-starting is met (see Table 7). Patients whose dose is missed for reasons other than study drug related toxicity should receive this dose as soon as possible.

Patients may continue on treatment for any Grade 3 laboratory parameters that may be increased due to decreased clearance in the liver, for example, but not limited to, CK, LDH and transaminases (ALT/AST), if not associated with clinical signs and symptoms (see section 6.3.9.2.2 for details on expected asymptomatic decreases in hepatic clearance). Close monitoring of liver function parameters (including Total Bilirubin, Creatinine Kinase, LDH, AST, ALT, Alkaline Phosphatase, Albumin, GGT, aPTT/INR) is required to ensure that the asymptomatic increases in LFTs due to Emactuzumab are not masking signs of true liver damage due to other reasons. If ALT/AST elevation is 3x ULN in combination with elevation in T Bili above 2.0x UNL patient has reached threshold for Hy's Law and all treatment will be permanently discontinued. Refer to Table 7 and section 6.3.9.2.2 for management guidelines for hepatic events and Emactuzumab dose reduction schedule and Table 8 for management of Dermatological toxicities and dose reduction schedule.

A patient with any $\geq$ Grade 3 electrolyte, calcium, phosphorus, or magnesium abnormality which does not correct to $\leq$ Grade 1 within 14 days with adequate repletion, must be discussed with the principal investigator to determine subject removal. For any other non-Hematological $\geq$ Grade 3 toxicities not listed above, believed to be related to Emactuzumab, the investigator will hold the dose of Emactuzumab until toxicity reverts to ≤ grade 1 within a maximum of 21 days at which point the patient will be removed from treatment with Emactuzumab and can continue with Paclitaxel and Bevacizumab.

For any Grade 4 hematological toxicity related to study therapy, study therapy will be held until toxicity reverts to ≤ grade 1 within a maximum of 21 days at which point the patient will be removed from treatment with Emactuzumab and can continue with Paclitaxel and Bevacizumab.

6.3.9.1 During the Infusion

6.3.9.1.1 Infusion-Related Reactions

Infusion-related reactions may be clinically indistinguishable from allergic/anaphylactic reactions. Allergic/anaphylactic reactions have occurred following administration of proteins to patients. Medication

(including epinephrine for subcutaneous injection, corticosteroids, diphenhydramine for i.v. injection) and resuscitation equipment should be available for immediate use. If an infusion-related reaction (allergic reaction/hypersensitivity, fever, chills, pain, bronchospasm, wheezing or hypoxia) develops, the infusion should be temporarily slowed down or interrupted. Refer to Table 5 for guidance on the management of infusion-related reactions.

Part 1 and Part 2B: In the case of a stop or interruption of *Emactumuzab* infusion due to adverse events (e.g. infusion reaction) the end of infusion will be determined per the guidelines below:

- If an infusion related reaction causes an infusion interruption, and Emactuzumab is able to be restarted and completed, then the time of Emactuzumab completion will be considered the end of infusion.

- If an infusion related reaction causes an infusion interruption, and the reaction does not resolve causing an incomplete treatment, then the time Emactuzumab was interrupted will be considered the end of infusion.

TABLE 5: MANAGEMENT OF INFUSION RELATED REACTIONS DURING TREATMENT WITH EMACTUZUMAB

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing

	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Infusion related guidance:

If a patient develops a grade 1 infusion reaction, the infusion rate should be slowed down by up to 50%. Patient should be monitored closely until complete resolution of the symptoms. Upon resolution of symptoms, the infusion rate may be re-escalated to 100% after an observation time of 30 minutes.

If a patient develops a grade 2 infusion reaction, infusion should be slowed down by 50% or interrupted. Patient should be monitored closely until complete resolution of the symptoms and treated as clinically indicated. If a patient promptly responds as per the investigator, to medical intervention, the infusion may be restarted at 50% of the previous infusion rate and the infusion rate may be re-escalated to 100% after an observation time of 30 minutes and in the absence of recurrence of infusion-related symptoms. If the infusion cannot be restarted the infusion should be repeated if the patient received ≤ 50% of scheduled dose and the IRR has resolved completely. In the event that >50% of the dose was received prior to interruption, the infusion may be repeated at the investigator's discretion. The actual dose received on each occasion should be documented in the eCRF.

If a ≥ Grade 3 infusion reaction occurs during the infusion, the infusion should be stopped immediately and not re-started. The patient should be monitored closely until complete resolution or stabilization of the symptoms and receive appropriate treatment as clinically indicated. The actual dose received on each occasion should be documented in the eCRF.

With the exception of any grade 3 or 4 infusion reaction, patients may resume treatment when the infusion reaction resolves. Hypersensitivity reactions will be considered as treatment limiting toxicities and not dose-limiting toxicities.

6.3.9.2 After Infusion

6.3.9.2.1 Management of Diarrhea

All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

Patients should receive clear instructions regarding the treatment of diarrhea and the necessity to contact the treating physician. To avoid complications of diarrhea such as electrolyte imbalance, dehydration, and renal dysfunction, early intervention with loperamide should be started for diarrhea ≥ Grade 1. Patients should receive loperamide capsules 4 mg followed by 2 mg with every unformed stool. The maximum daily

dose of loperamide should not exceed 16 mg. Loperamide can be stopped after the patient is free of diarrhea for 12 hours. Electrolyte repletion and i.v. fluids should be administered on an as needed basis.

If diarrhea is reported frequently as an adverse event, investigators may also consider premedicating patients with loperamide prior to start of emactuzumab infusion.

- If a patient in Part I of the trial experiences Grade 3-4 diarrhea for >2 days, despite adequate treatment (defined as a SAE), no further doses will be administered and the patient will be observed for resolution of toxicity.

See below in table 6, a summary of dose-delay criteria for diarrhea (if occurring despite adequate treatment and considered related to the study medication):

TABLE 6: DOSE-DELAY CRITERIA FOR DIARRHEA DURING TREATMENT WITH EMACTUZUMAB

	Grade 2	Grade 3	Grade 4 (or SAE)
1st occurrence	Delay infusion for up to 2 weeks. Resolution to ≤ G1: continue at same dose. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. If diarrhea persists greater than 3 days, administer oral corticosteroids. No resolution to ≤ G1: discontinue medication	IV hydration is required. Delay infusion for up to 2 weeks. Resolution to ≤ G1: continue at same dose. When symptoms improve to grade 1 or less steroid taper should be started and continued over no less than 4 weeks. If diarrhea persists greater than 1 week, treat with intravenous steroids followed by high dose oral steroids. No resolution to ≤ G1: discontinue medication	IV hydration is required. Discontinue medication
2nd occurrence	Delay infusion for up to 2 weeks. Resolution to ≤ G 1 continue at same dose. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	Delay infusion for up to 2 weeks. Resolution to ≤ G1: continue at same dose. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	

	Grade 2	Grade 3	Grade 4 (or SAE)
	If diarrhea persists greater than 3 days, administer oral corticosteroids. No resolution to ≤ G1: discontinue medication	If diarrhea persists greater than 1 week, treat with intravenous steroids followed by high dose oral steroids. No resolution to ≤ G1: discontinue medication	
3rd occurrence	Delay infusion for up to 2 weeks. Resolution to ≤ G 1 continue at same dose. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. If diarrhea persists greater than 3 days, administer oral corticosteroids. No resolution to ≤ G1: discontinue medication	Discontinue medication	
4th occurrence	Discontinue medication		

6.3.9.2.2 Management Guidelines for Hepatic Events

Inhibitors of CSF-1R have been associated with depletion of Kupffer cells in the liver. Kupffer cells play an important role in the clearance of serum enzymes, including AST, ALT, LDH, and CK. Increased levels of AST, ALT, LDH, and CK have been observed in patients treated with emactuzumab. In the majority of patients, the increase in AST, ALT, LDH, and CK level was 2- to 3-fold above baseline. Patients who experienced an elevation in liver enzymes remained asymptomatic; laboratory work up revealed no evidence for damage to the liver. Therefore, the observed elevation in liver enzyme levels is consistent with delayed clearance of liver enzymes secondary to emactuzumab-induced inhibition of Kupffer cells.

However, in combination with bevacizumab and paclitaxel patients may experience a true liver toxicity which could be masked by emactuzumab mediated AST, ALT, LDH, and CK elevations. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin, PT and INR (levels are independent of emactuzumab mediated depletion of Kupffer cells) as well as hepatic transaminases, and liver function will be monitored throughout study treatment.

In patients treated with emactuzumab, bilirubin, alkaline phosphatase, and PT/PTT remain within normal range; thus, elevations in these liver function parameters should prompt a work-up for hepatocyte damage. Similarly, large increases in CK and LDH are also commensurate with emactuzumab-induced Kupffer cell depletion; thus, in the absence of elevations of bilirubin, alkaline phosphatase and PT/PTT, elevations in these two parameters do not reflect damage to the liver.

While in this study, patients who present with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs to include AST, ALT, LDH, CK, alkaline phosphatase, PT, INR, albumin and bilirubin) performed immediately and reviewed before administration of the next dose of study drug.

If LFTs increase, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered.

Guidelines for the management of liver toxicity during treatment with emactuzumab plus bevacizumb and paclitaxel are provided below in Table 7.

TABLE 7: GUIDELINES ON THE MANAGEMENT AND REPORTING OF ELEVATED LIVER ENZYMES DURING TREATMENT WITH EMACTUZUMAB

Toxicity NCI CTCAE Grade	Paclitaxel	Bevacizumab	Emactuzumab	Reporting
ALT/AST (u/L)				
Grade 1: (>ULN – 3.0x ULN) Grade 2: (>3.0x – 5.0x ULN)	Continue study treatment			No action
Grade 3: (>5.0x – 20.0x ULN)	Hold all treatment; investigate to exclude alternate causes of abnormal LFTs. To rule-out autoimmune etiology consider Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-LKM, and anti−smooth muscle antibody tests. Repeat lab work daily, when investigator has assessed alkaline phosphatase, bilirubin and PT/PTT as stable, resume treatment at one dose reduction with weekly labs.			If asymptomatic and INR, PT, alkaline phosphatase, total bilirubin within normal range: attributed to Kupffer cell depletion and will not be reported as a serious adverse event. If symptomatic and abnormal PT, INR, alkaline phosphatase and/or bilirubin increases hold all treatment: expedited reporting as serious adverse event and assess causality. DLT in Part 1 if unable to restart in 21 days.
Grade 4: (>20.0x ULN)	Hold all treatment; investigate to exclude alternate causes of abnormal LFTs. To rule-out autoimmune etiology consider Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-LKM, and anti−smooth muscle antibody tests. Repeat lab work daily, when investigator has assessed alkaline phosphatase, bilirubin and PT/PTT as stable,			If asymptomatic and INR, PT, alkaline phosphatase, total bilirubin within normal range: attributed to Kupffer cell depletion and will not be

	resume treatment at one dose reduction with weekly labs.	reported as a serious adverse event. If symptomatic and abnormal PT, INR, alkaline phosphatase and/or bilirubin increase hold all treatment: expedited reporting as adverse event. DLT in Part 1 if unable to restart in 21 days.

Bilirubin (mg/dL)		
Grade 1: (ULN – 1.5x ULN)	Continue study treatment	No action
Grade 2: (1.5x – 2.0x ULN) Above 2.0x ULN meets criteria for Hy's Law if Grade 2 or higher ALT/AST	Continue study treatment. Investigator review lab work, AST/ALT	Monitor lab work every day until assessed as stable by investigator.
Grade 2: (Hy's Law) 2.0 – 3.0x ULN Grade 3: (3.0x – 10.0x ULN)	Hold treatment. Consult Hepatology.	Discontinue all treatment. Monitor liver function tests daily until assessed as stable by investigator.
Grade 4: (>10.0x ULN)		
CK (u/L) (CPK)		
Grade 1: (ULN – 2.5x ULN)	Continue study treatment	No action
Grade 2: (2.5x – 5.0x ULN)		Monitor weekly lab work.

Grade 3: (5.0x – 10.0x ULN)	Continue study treatment with daily alkaline phosphatase, bilirubin and PT/PTT until investigator assesses as stable, then monitor weekly lab work.			If asymptomatic and INR, PT, alkaline phosphatase, total bilirubin within normal range: attributed to Kupffer cell depletion and will not be reported as a serious adverse event. If symptomatic and/or abnormal PT, INR, alkaline phosphatase and/or bilirubin increases hold all treatment: expedited reporting as serious adverse event and assess causality.
Grade 4: (> 10.0x ULN)	Continue study treatment on Part 2B with daily alkaline phosphatase, bilirubin and PT/PTT until investigator assesses as stable, then monitor weekly lab work. Part 1 hold all treatment Resume Emactuzumab at one dose reduction when levels resolve to ≤ grade 2	Continue study treatment on Part 2B with daily alkaline phosphatase, bilirubin and PT/PTT until investigator assesses as stable, then monitor weekly lab work. Part 1 hold all treatment Resume Emactuzumab at one dose reduction when levels resolve to ≤ grade 2	Hold treatment on Part 2B with daily alkaline phosphatase, bilirubin and PT/PTT until investigator assesses as stable. Resume Emactuzumab at one dose reduction when levels resolve to ≤ grade 2 with weekly labs. On Part 1 hold all treatment Resume Emactuzumab at one dose reduction when levels resolve to ≤ grade 2	If asymptomatic and INR, PT, alkaline phosphatase, total bilirubin within normal range: attributed to Kupffer cell depletion and will not be reported as a serious adverse event. If symptomatic and/ or abnormal PT, INR, alkaline phosphatase, and/or bilirubin increase hold all treatment: expedited reporting as adverse event. . DLT in Part 1 if unable to restart within 21 days.
LDH (u/L)				
Grade 1: ULN-2.5x ULN Grade 2: 2.5xULN-5.0x ULN	Continue study treatment			No action
Grade 3: 5.0xULN-20.0x ULN	Hold all treatment. Monitor lab alkaline phosphatase, bilirubin and PT/PTT daily until stable, then resume Emactuzumab at one dose reduction when levels resolve to ≤ grade 2 with weekly labs.			Investigator to assess lab work, stable patient will be followed with weekly lab work and may be treated after AST, ALT, PT, PTT,

		alkaline phosphatase, total bilirubin reviewed by investigator
Grade 4: Above 20.0x ULN	Hold all treatment. Monitor lab alkaline phosphatase, bilirubin and PT/PTT daily until stable, then resume Emactuzumab at one dose reduction when levels resolve to ≤ grade 2 with weekly labs.	In Part 2B: daily lab work until stable, then weekly. If stable, may restart treatment after clearance by investigator and medical monitor & AST, ALT, PT, INR, alkaline phosphatase, bilirubin within normal limits. DLT in Part 1 in unable to restart 21 days

Investigations should be conducted to exclude alternate causes of the abnormal LFTs, e.g.. progression of underlying disease, infections or other diseases affecting liver function, concomitant medication and nutrition. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-LKM, and anti-smooth muscle antibody tests should be evaluated if an autoimmune etiology is considered.

For patients with documented liver metastasis and elevated LFT results at baseline, further elevations of LFT results may not require dose interruptions if there are no progressive changes in the ALT and/or AST (less than a doubling) and if there are no progressive elevations in total bilirubin or INR. Regular monitoring of LFTs, bilirubin, coagulation parameters will be conducted throughout the study. Please refer to the Schedule of Assessments.

Patients who, upon restarting study treatment after resolution, experience another dose delay due to elevations of LFTs with concomitant increase of bilirubin and/or abnormal coagulation parameters should permanently discontinue treatment.

Study treatment should be discontinued for life-threatening immune study related hepatic events.

6.3.9.2.3 Neutrophil Count

If a patient experiences an Absolute Neutrophil Count (ANC) of ≤ 1.5 x 10^9/L prior to any infusion, the patient will be observed and the infusion will be delayed for up to 3 weeks until resolution.

6.3.9.2.4 Periorbital Edema

Periorbital edema has been documented in agents that interfere with the CSF-1 pathway. In the GLP toxicology study, treatment-related periorbital swelling was noted in all except two dosed animals. This finding persisted through recovery. Histologically, only edema was noted, with no inflammatory infiltrates or endothelial alterations. No specific therapy is required for mild periorbital edema in patients receiving Emactuzumab, however, cold eye cell eye masks may be used during infusion and at night. In more severe cases, a short pulse of diuretics and occasional use of topical treatment with 1% hydrocortisone plus 0.25% phenylephrine may be beneficial. Symptomatic patients may be referred to an ophthalmologist for further examination.

6.3.9.2.5 Dermatologic Toxicity

Treatment with emactuzumab may cause dermatologic toxicity in some patients. In some patients who developed skin rash under treatment with emactuzumab, further workup disclosed a diagnosis of cutaneous lupus erythematosus. In an attempt to reduce the risk of dermatologic toxicity, patients may consider the following precautions:

- Patients should be advised to avoid manipulation of lesions, as this may potentially induce new skin lesions.
- Patients should avoid sun exposure and use sunscreens effective against ultraviolet A and ultraviolet B irradiation. Sufficient amounts of sunscreen with a sun protection factor of at least 50 should be applied 20−30 minutes prior to expected exposure. Physical sunscreens, such as titanium dioxide or zinc oxide, provide broad-spectrum protection.
- Patients should be advised to avoid tanning studios, sunbathing, and outdoor activities. It is important to consider the risk of vitamin D deficiency in sun-avoiding patients, as sunlight is required for vitamin D synthesis. 25-Hydroxyvitamin D levels may be monitored and supplementation with at least 400 IU of vitamin D3, or cholecalciferol may prevent vitamin D deficiency.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be performed unless contraindicated. Low-grade rash and pruritus immune-related adverse events have been treated with symptomatic therapy (e.g., antihistamines).

Guidelines for the management of dermatologic toxicity are provided in Table 8 below.

TABLE 8: MANAGEMENT GUIDELINES FOR POTENTIAL DERMATOLOGICAL TOXICITY/ RASH DURING TREATMENT WITH EMACTUZUMAB

Toxicity	Description	Management

Dermatologic toxicity/rash (e.g. maculopapular or purpura)	Grade 1 mild < 10% BSA	• Continue all study treatment. Symptomatic therapy with antihistamine PRN. • Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2 moderate 10%−30% BSA	• After Cycle 1 toxicity assessment period: hold all study medication until resolved to Grade 1 or baseline then resume one dose level lower of Emzactuzumab. • Consider dermatologist referral. • Administer topical steroids. • Consider higher potency topical steroids if rash unresolved.
	Grade 3 severe > 30% BSA	• Hold all study treatment • Consult dermatologist. • Administer oral prednisone 10 mg or equivalent. If rash unresolved after 48−72 hours, administer oral prednisone 60 mg or equivalent. • Restart Bevacizumab and Taxol at previous dose and reduce one dose level of Emactuzumab if rash resolved and systemic dose is ≤10mg oral prednisone equivalent per day.
	Grade 4 skin toxicity:	• Permanently discontinue *emactuzumab* for life-threatening immune-related dermatologic toxicity. Continue Paclitaxel and Bevacizumab
BSA = body surface area; PRN = as needed.		

6.4 Bevacizumab

Bevacizumab will be obtained from the institutional pharmacy through standard mechanisms.

Formulation/packaging/storage

Per manufacturer's guidelines.

Product preparation
Per manufacturer's guidelines.

Dose administration
Per manufacturer's guidelines.
Bevacizumab is manufactured by recombinant DNA technology, using a genetically engineered Chinese hamster ovary (CHO) cell line. The protein is purified from the cell culture medium by routine methods of column chromatography and filtration. The final product is tested for quality, identity, safety, purity, potency, strength, and excipient/chemical composition according to International Conference on Harmonisation (ICH) guidelines. The purity of bevacizumab is > 95%.

Bevacizumab may be supplied in 6-cc (100-mg) and 20-cc (400-mg) glass vials containing 4 mL or 16 mL of bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI). Vials contain no preservative and are suitable for single use only. For further details and molecule characterization, see the bevacizumab Investigator Brochure.

6.4.1 Bevacizumab Administration

Bevacizumab should be prepared using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% Sodium Chloride Injection, USP. Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration.

The initial dose will be delivered over 90±15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±10 minutes.

If a patient experiences a grade 1 or 2 infusion–associated adverse event, she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the patient continues to be premedicated. If a patient experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90±15 minutes. Similarly, if a patient experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

6.4.2 Bevacizumab Storage

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Keep vial in the outer carton due to light sensitivity.

VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C–30°C in 0.9% Sodium Chloride solution. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in a controlled and validated aseptic conditions.

Body weight at baseline is to be used to calculate the required dose, and no dose modifications are foreseen unless the patient's body weight changes by ± 10% from baseline.

A rounding up or down of the dose is acceptable to allow practical ease of administration. Rounding of the dose is optional and if the treating physician decides to round the total dose of bevacizumab, it should be rounded to the nearest 5 mg.

The bevacizumab dose (10 mg/kg) should not be reduced or modified due to toxicity.

6.4.3 Management of Bevacizumab Toxicities

In cases of toxicity, please refer to the latest version of the bevacizumab Investigator Brochure for guidance.

As described below, bevacizumab treatment may be either temporarily or permanently suspended in the case of hypertension, proteinuria, thrombosis/embolism, hemorrhage, CHF or wound healing complications in addition to any other serious bevacizumab-related toxicity (grade 3 or 4). Bevacizumab should be temporarily withheld in the event of febrile grade 4 neutropenia and/or grade 4 thrombocytopenia (regardless of the relationship to treatment), since these conditions are predisposing factors for an increased bleeding tendency. In general, appropriate management for grade 3 or 4 bevacizumab-related events is described in Table 9. Additionally, guidance on the management of infusion related reactions is described in Table 5.

TABLE 9 MANAGEMENT OF GRADE 3 OR 4 BEVACIZUMAB-RELATED AES

First occurrence	Permanently discontinue bevacizumab treatment
Second occurrence	

In addition, bevacizumab treatment should be permanently discontinued in patients experiencing any of the following events:

- Reversible Posterior Leucoencephalopathy Syndrome (RPLS).
- Grade 3/4 hemorrhagic/bleeding events.
- Grade 4 venous thromboembolism
- Any grade CNS bleeding
- Any grade of arterial thromboembolism.
- Grade 4 hypertension (hypertensive crisis).
- Grade 4 proteinuria (nephrotic syndrome).
- Grade 3/4 left ventricular dysfunction (CHF).
- Any grade of gastrointestinal perforation.
- Any grade of tracheo-esophageal fistula.
- Grade 4 non-gastrointestinal fistula.
- Grade ≥ 2 hemoptysis (hold temporarily or permanently discontinue)

6.4.3.1 Reversible Posterior Leucoencephalopathy Syndrome

There have been rare reports of patients treated with bevacizumab that develop signs and symptoms consistent with RPLS, a rare neurological disorder, which can present with following signs and symptoms among others: seizures, headache, confusion, visual disturbance or cortical blindness, with or without

associated hypertension. Brain imaging confirms the diagnosis of RPLS. Bevacizumab treatment should be discontinued in patients who develop signs/symptoms consistent with RPLS and the specific symptoms should be appropriately treated, including control of hypertension.

6.4.3.2 CNS Bleeding

Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding of any grade. Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS hemorrhage in such patients has not been prospectively evaluated in randomized clinical studies. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding of any grade.

6.4.3.3 Hypertension

Patients must be closely monitored on study for the development or worsening of hypertension. Blood pressure measurements should occur after the patient has been in a resting position for ≥5 minutes. If the initial BP reading is ≥140 mmHg systolic and/or ≥90 mmHg diastolic pressures, the result should be verified with a repeat measurement. If hypertension occurs, bevacizumab treatment should be managed as described in Table 10.

TABLE 10. BEVACIZUMAB TREATMENT MANAGEMENT FOR HYPERTENSION

NCI CTCAE v4.03 grading	Hypertension pattern	Treatment action
Grade 1	Prehypertension (systolic BP 120-139 mm Hg or diastolic BP 80-89 mm Hg)	Give bevacizumab.
Grade 2	Stage 1 hypertension (systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated	Withhold bevacizumab and all treatment. Start antihypertensive therapy. Once BP is <150/100 mmHg, patients may continue bevacizumab therapy.
Grade 3	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one anti-hypertensive drug or more intensive therapy than previously used indicated.	Hold bevacizumab and all treatment for persistent or symptomatic hypertension and discontinue permanently if hypertension is not controlled according to Investigator judgment.
Grade 4	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurological deficit,	Permanently discontinue bevacizumab.

	hypertensive crisis); urgent intervention indicated	

6.4.3.4 *Proteinuria*

Proteinuria will be assessed within 48 hours before each bevacizumab treatment by dipstick method unless assessed by 24-hour urine collection. Alternatively, proteinuria testing can be performed according to local standards. Proteinuria should be managed according to Table 11 below.

TABLE 11. BEVACIZUMAB TREATMENT MANAGEMENT FOR PROTEINURIA

NCI CTCAE v4.03 grading	Proteinuria Pattern	Treatment action
Grade 1	1+ proteinuria; urinary protein <1.0 g/24 hrs	No bevacizumab dose modifications
Grade 2	2+ proteinuria; urinary protein 1.0-3.4 g/24 hrs	Suspend bevacizumab and all treatment for urine protein level ≥ 2 g/24 hrs and resume when proteinuria is < 2 g/24 hours. For 2+ dipstick: may administer bevacizumab; obtain 24-hour protein urine prior to next bevacizumab dose. For 3+ dipstick: obtain 24-hour urine prior to bevacizumab administration.
Grade 3	Urinary protein >=3.5 g/24 hrs	Suspend bevacizumab and all treatment. Resume when proteinuria is < 2 g/24 hrs, as determined by 24-hrs urine collection < 2 g.
Grade 4 (Nephrotic syndrome)	-	Permanently discontinue bevacizumab.

If bevacizumab treatment is delayed for more than 2 cycles, continuation of treatment must be discussed with the Genentech medical monitor or designee.

Nephrotic syndrome: Bevacizumab must be permanently discontinued if nephrotic syndrome (grade 4 per NCI CTCAE v4.03) is detected at any time.

6.4.3.5 *Dose interruption due to infusion-associated reactions*

If ≤ grade 3 infusion-associated reaction (cytokine release syndrome/acute infusion reaction or allergic reaction/hypersensitivity such as fever, rash, urticaria or bronchospasm) occurs, pre-medication should be given with the next dose, but the infusion time may not be decreased for the subsequent infusion. If the next dose is well-tolerated with pre-medication, the subsequent infusion time may be decreased by 30 ±10 minutes as long as pre-medication continues to be used. If infusion-related AEs occur with the

60-minute infusion, all subsequent doses should be given over 90 ±15 minutes (with pre-medication). If infusion-related AEs occur with the 30-minute infusion, all subsequent doses should be given over 60 ± 10 minutes (with pre-medication). For patients with grade 3 or 4 reactions, the bevacizumab infusion should be permanently discontinued.

6.4.3.6 Surgical procedures and wound healing complications

Bevacizumab therapy should be withheld for an interval of at least four weeks (28 days) before conducting elective surgery. In the case of unplanned surgical procedures, bevacizumab should be stopped as soon as the indication for surgery is identified. Emergency surgery should be performed as appropriate without delay after a careful risk benefit assessment.

Bevacizumab therapy should be restarted ≥28 days and ≤42 days following major surgery. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. If the wound is not fully healed within 42 days, bevacizumab treatment should be discontinued.

Continuation of study treatment in patients who have had bevacizumab therapy delayed for more than 2 treatment cycles due to surgical procedures or wound healing must also be discussed with the Genentech medical monitor or his/her designee.

6.4.3.7 Thrombosis/embolism

Arterial thromboembolism: If a patient experiences any grade of arterial thromboembolism during the study treatment period, bevacizumab should be discontinued permanently.
A history of arterial thromboembolic events or age greater than 65 years has been associated with an increased risk of arterial thromboembolic events during bevacizumab therapy. Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism and age greater than 65 years have a higher risk. Caution should be taken when treating these patients with bevacizumab.

Venous thromboembolism:
Bevacizumab should be held in patients developing a grade 3 thrombosis/embolism. Bevacizumab may be resumed once the patient is adequately anti-coagulated and on a stable level of anticoagulation for at least 2 weeks prior to restarting study drug treatment. Patients on heparin treatment should have an aPTT between 1.5-2.5 x ULN (or patient value before starting heparin treatment). Patients on coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1-4 days apart. Patients on full dose low molecular weight heparins should receive the appropriate dose based on the weight of the patient according to package insert.

An increased risk of venous thromboembolic events and bleeding in patients receiving anti-coagulation therapy after first venous thromboembolic event while receiving bevacizumab has been observed.
In the event of recurrent grade 3 thrombosis/embolism, the patient should be discontinued from bevacizumab.

Bevacizumab should be discontinued in patients with life-threatening (grade 4) pulmonary embolism.

6.4.3.8 Hemorrhage

An increased incidence of bleeding events was observed in study patients treated with bevacizumab as compared to control treatment arms. The hemorrhagic events observed in bevacizumab studies were predominantly tumour-associated hemorrhage and minor mucocutaneous hemorrhage.

If grade 3 or 4 bleeding of any kind occurs during the study treatment period bevacizumab should be permanently discontinued.
If hemorrhagic complications occur in patients on full dose anticoagulation therapy, permanently discontinue bevacizumab treatment and follow guidelines of the institution. Standard procedures such as antagonization with protamine or vitamin K, infusion of vitamin K dependent factors or insertion of a vena cava filter should be considered dependent on the severity of the bleeding and thrombotic events and the organ affected.
Bevacizumab should be temporarily held or permanently discontinued for grade ≥ 2 haemoptysis (defined as ≥ 2.5 mL bright red blood per episode). The safety of re-initiating bevacizumab in patients previously experiencing grade ≥ 2 haemoptysis has not been evaluated.

6.4.3.9 Gastrointestinal Perforation and Fistula

Bevacizumab has been associated with serious cases of GI perforation in patients with mCRC and a few reports of gallbladder perforation have been reported from the post-marketing experience. The presentation of these events has varied in type and severity, ranging from free air seen only on the plain abdominal X-ray, which resolved without treatment, to a colonic perforation with abdominal abscess and fatal outcome. The common feature among these cases was intra abdominal inflammation, either from gastric ulcer disease, tumour necrosis, diverticulitis or chemotherapy-associated colitis. Nevertheless, a causal association of an intra-abdominal inflammatory process and GI perforation to treatment with bevacizumab has not been established. However, caution should be exercised when treating patients with intra-abdominal inflammatory process with bevacizumab.

Bevacizumab should be permanently discontinued in patients who develop GI perforation.

Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae within the GI tract or GI tract and skin are common in patients with mCRC and ovarian cancer, but are uncommon or rare in other indications. Other fistulae (e.g. tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly in bevacizumab clinical trials patients and in post-marketing reports.

Temporarily discontinue bevacizumab in patients with grade 2 or 3 non- tracheoesophageal fistula until resolution to ≤ grade 1.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistula or any grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

6.4.3.10 Congestive Heart Failure

Events consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF, requiring treatment or hospitalisation. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, concomitant cardiotoxic therapy or CHF with bevacizumab.

Bevacizumab should be permanently discontinued in patients with ≥ grade 3 CHF.

6.4.3.11 Hypersensitivity/Allergic Reactions and Infusion-Associated Reactions

Bevacizumab should be permanently discontinued in patients exhibiting hypersensitivity/allergic reactions.

The NCI CTCAE distinguish between hypersensitivity reactions and acute infusion reactions induced by cytokine release. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms associated with these reactions overlap.

Patients may be at risk of developing infusion reactions to bevacizumab. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If an infusion reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

6.4.3.12 Osteonecrosis of the Jaw

Osteonecrosis of the jaw was reported in patients receiving bevacizumab mainly in combination with bisphosphonates in the post-marketing setting. The pathogenesis of the osteonecrosis is unclear. For further information, please refer to the Avastin® Investigator' Brochure.

6.5 Paclitaxel

Paclitaxel will be obtained from the institutional pharmacy through standard mechanisms.

Formulation/packaging/storage
Per manufacturer's guidelines.

Product preparation
Per manufacturer's guidelines.

Dose administration
Per manufacturer's guidelines.

6.5.1 Dose Modifications

Up to 2 dose reductions (70mg/m^2 and 60mg/m^2) are acceptable for paclitaxel. For patients who have one dose omitted in one cycle of treatment, the patient may be maintained at 70mg/m^2 for 1-hour i.v. infusion in subsequent cycles. If there is a second omission, then the second dose reduction of 60 mg/m^2 for 1-hour i.v. infusion will be allowed.

6.5.2 Management of Paclitaxel Toxicities

6.5.2.1 Hematological toxicity

Dose reductions for next course will be performed according to following guidelines for nadir:

TABLE 12. SUMMARY OF PACLITAXEL DOSE REDUCTIONS

WBC [10^9/L]	ANC[1] [10^9/L]	Platelets [10^9/L]	Dose modification
< 1.0 lasting > 7 days	< 0.5 lasting > 5 days	< 25	Decrease 1 dose level
Febrile Neutropenia[2]		Severe bleeding	Decrease 1 dose level
Febrile Neutropenia[2]		Severe bleeding	Discontinue paclitaxel

1. ANC - Absolute Neutrophil Count

2. Febrile neutropenia: Fever > 38,5°C associated with ANC < 1.0 x 10^9/L

Hematological recovery (values at day of scheduled retreatment)
The WBC count must be ≥ 3.0 x 10^9/L or ANC ≥ 1.0 x 10^9/L and the platelet count ≥ 80 x 10^9/L prior to the beginning of the following course of treatment. For patients who do not achieve hematological recovery on scheduled day of the course, complete blood counts should be performed twice weekly until the above defined limits are achieved.
If hematological recovery is achieved within 14 days after the scheduled day of the course, the full dose of paclitaxel adjusted for the previous nadir should be administered immediately.
If hematological recovery is not achieved 14 days or more after the scheduled day of the course, the patient will discontinue treatment.
Administration of G-CSF or EPO is permitted according to approved indications and scientific recommendations.

6.5.2.2 Non-hematological toxicity

6.5.2.2.1 Mucositis and cutaneous toxicity

The occurrence of mucositis CTCAE grade > 2 leads to a dose reduction of one level.

6.5.2.2.2 Neurological toxicity

In case of:
- CTCAE grade 2: Reduce dose of one level.
- CTCAE grade 3/4: Withhold paclitaxel treatment and follow patient as per protocol.

6.5.2.2.3 Hypersensitivity premedication

Premedication prior to paclitaxel should be administered in accordance with local standard of care in order to prevent grade 3 or higher hypersensitivity reactions. An example of premedication is as follows:

Dexamethasone	20 mg IV	30 minutes prior to paclitaxel
Clemastine *	2 mg IV	30 minutes prior to paclitaxel
Ranitidine *	50 mg IV	30 minutes prior to paclitaxel
5HT3 Antagonist *	Single dose IV	30 minutes prior to paclitaxel

*Alternative compounds of the same classes can be used

Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.

Significant hypersensitivity reactions as characterised by dyspnoea and hypotension requiring treatment, angioedema, and generalised urticaria have occurred in <1% of patients receiving paclitaxel after adequate premedication. These reactions are probably histamine-mediated.

In the case of grade 3 or higher hypersensitivity reactions, paclitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with paclitaxel.

Thirty-four percent of patients receiving paclitaxel (17% of all courses) experienced minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.

6.5.2.2.4 Other Major Organ Toxicity (not evaluated as disease related)

If the patient has any clinically significant non-hematological drug related toxicity CTCAE grade ≥ 3, the treatment course will be delayed until the toxicity is no longer clinically significant or the patient will go off protocol treatment according to investigator evaluation. In case of absence of recovery from

hematological and non-hematological toxicity for 2 weeks or more (counted from planned day 1 of treatment course) the patient will go off protocol treatment and will be followed up as any other patient.

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 AEs and laboratory abnormalities

7.1.1 Clinical AEs

In accordance with the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation patient who receives a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment to be known as an AE. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during a study are to be reported as AEs. The investigator or physician designee is responsible for providing source documentation and assigning attribution for all AEs.

7.1.1.1 Intensity

The Intensity of AEs are usually graded according to the NCI Common Toxicity Criteria for Adverse Events v 4.03 (CTCAE) on a five-point scale (grade 1–5). In this study, AEs grade 2–5 occurring during the study and up to 30 days after the last dose of study medication will need be recorded in the eCRF. AEs not listed on the CTCAE should be graded as follows:

TABLE 13. GRADING OF AES ACCORDING TO NCI CTCAE V 4.03

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity.
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient.
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life threatening/disabling	An immediate threat to life or an event that leads to permanent mental or physical conditions that prevents work or the performance of normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death.

7.1.1.2 Drug – AE relationship

The causality relationship of the (combination of) study drug to the AE will be assessed by the investigator as either:

Yes or No

If there is a reasonable, suspected, causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, a drug-event relationship should be assessed as **Yes**.
The following criteria should be considered in order to assess the relationship as **Yes**:

- Reasonable temporal association with drug administration.
- It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- Known response pattern to suspected drug.
- Disappears or decreases on cessation or reduction in dose.
- Reappears on rechallenge.

The following criteria should be considered in order to assess the relationship as **No**:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

7.1.1.3 SAEs (immediately reportable to Genentech/Genentech)

A SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfils at least one of the following criteria:

- It is fatal; (results in death; NOTE: death is an outcome, not an event).
- Life-threatening; (NOTE: the term "Life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- Required in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above.

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

7.1.1.4 Progression of underlying malignancy

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.
Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease

progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.
If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

7.1.2 Treatment and follow-up of AEs

After at least 30 days following the last study drug intake/administration, continue to follow up AEs (grades 2–5) every 2 months as follows:
Related AEs: Follow until one of the following occurs:

- Resolved or improved to baseline.
- Relationship is reassessed as unrelated.
- Death.
- Start of new anti-cancer regimen.
- Investigator confirms that no further improvement can be expected.
- Clinical or safety data will no longer be collected or final database closure.

Unrelated severe or life threatening AEs: Follow until one of the following occurs:

- Resolved or improved to baseline.
- Severity improved to grade ≤2.
- Death.
- Start of new anti-cancer regimen.
- Investigator confirms that no further improvement can be expected.
- Clinical or safety data will no longer be collected or final database closure.

Unrelated grade 1 AEs: These events should be managed in accordance with local practice; however, they are not recorded in the eCRF. The final outcome of each AE must be recorded on the eCRF.

7.1.3 Laboratory test abnormalities

Laboratory tests should be performed as per local standard of care. Laboratory test results of ≥grade 2, or clinically significant results, will be recorded on the Adverse Events pages of the eCRF.
Any laboratory result abnormality fulfilling the criteria for a SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

Not every laboratory abnormality qualifies as an adverse event. Clinically significant treatment-emergent abnormal laboratory results are those meeting one or more of the following conditions:

- Accompanied by clinical symptoms.
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation).
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal (ULN) associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study medication, which falls outside the laboratory reference range and meets the clinical significance criteria.

This does not apply to any abnormal laboratory result which falls outside the laboratory reference range but which does not meet the clinical significance criteria (which will be analysed and reported as laboratory abnormalities); those which are considered AEs of the type explicitly exempted by the protocol; or those which are a result of an AE which has already been reported.

7.1.3.1 Follow-up of abnormal laboratory test values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed until they have returned to the normal range, baseline value and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF for all grade 2–5 laboratory AEs.

7.2 Handling of safety parameters

7.2.1 Reporting of AEs

The investigator or qualified designee will be responsible for collecting and tracking all new or worsening protocol-defined AEs originating from the study in accordance with the schedule of assessments and more frequently if clinically indicated.

The investigator or qualified designee will be responsible for the evaluation of AEs originating from the Study for the Products. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03. All grade 2–5 related and unrelated AEs occurring during the study and up to 30 days after the last dose of study medication will be recorded on the AE page(s) of the eCRF and followed until resolution, or until adequate due diligence with regard to obtaining follow-up information. After 30-days post-treatment, AEs will not be collected unless they are serious/clinically relevant and are considered to be related to the study drug.

All AEs of unknown etiology associated with emactuzumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI).

MD Anderson PI will forward monthly listings of non-serious AEs originating from the study to the Genentech contact listed below:
Genentech Drug Safety at: (650)-225-4682 OR (650)-225-4630. Please use the "Genentech Safety Reporting Fax Cover Sheet" provided at the end of the protocol (see Appendix 7).

Emactuzumab Safety at: new_york.ml29802predcontactsd@Genentech.com

The investigator or qualified designee will ensure that all single case reports have been adequately received by Genentech, via the exchange of a de-identified periodic line-listing documenting single case reports in the preceding time period (monthly).

7.2.1.1 AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product

The Avastin Events of Special Interest are:

Hypertension ≥ grade 3
Proteinuria ≥ grade 3
GI perforation, abscesses and fistulae (any grade)
Wound healing complications ≥ grade 3
Haemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis)
Arterial thromboembolic events (any grade)
Venous thromboembolic events ≥ grade 3
PRES (any grade)
CHF ≥ grade 3
Non-GI fistula or abscess ≥ grade 2

7.2.1.1.1 Special Situation Reports

Special situation reports
In addition to all AEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)
- Lack of therapeutic efficacy

In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

7.2.2 Reporting of SAEs (immediately reportable)

Any clinical AE or abnormal laboratory test value that is serious or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 30 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to study drug, must be reported to Genentech **within *one* working day** of the investigator becoming aware of the event (expedited reporting).

Non-serious Events of Clinical Interest will be forwarded by MD Anderson to Genentech and will be handled in the same manner as SAEs.

Additionally, any serious adverse events, considered by an investigator who is a qualified physician to be related to Genentech product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to Genentech.

TABLE 14 SAE COLLECTION BEFORE, DURING AND AFTER-STUDY DRUG DOSING

Before Investigational Medicinal Product dosing	Collect all SAEs occurring from the start of study screening procedures per the schedule of assessments Table 1.
During Investigational Medicinal Product dosing	Collect all SAEs occurring during use of the IMP.
After Investigational Medicinal Product dosing	Collect all SAEs from the last dose of the IMP up to 0 days, after last IMP dose taken. Collect all SAEs considered having a causal relationship to the IMP (as considered by the investigator), regardless of time elapsed since last IMP dose, even if study has stopped, including SAEs related to trial (study) procedures.
After Investigational Medicinal Product dosing, when the product is no more an Investigational Medicinal Product as per definition	SAEs are collected via spontaneous reporting procedures. However, if SAEs are received from patients that have participated in a clinical trial via the clinical study route *in error*, process the SAEs via the clinical study route as for clinical study SAEs.

Related SAEs ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.
Unrelated SAEs must be collected and reported during the study and for up to 30 days after the last dose of study medication.

The definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 will be adhered to. Complete information can be found in **Appendix 3.**

Serious adverse events (SAEs), and AEs of special interest (AESIs), where the patient has been exposed to the Products, will be sent on a Genentech Approved Site Specific Safety Reporting Form to the Genentech contact listed below. Transmission of these reports (initial and follow-up) will be either electronically or by fax and **within *one* working day** of the awareness date.

Genentech
Genentech Drug Safety at: (650)-225-4682 OR (650)-225-4630. Please use the "Genentech Safety Reporting Fax Cover Sheet" provided at the end of the protocol.

Emactuzumab Safety at: new_york.ml29802predcontactsd@roche.com

7.2.3 Reporting to Regulatory Authorities, Ethics Committees, and Investigators

Additional Reporting Requirements for IND Holders (if applicable): For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of emactuzumab. An unexpected adverse event is one that is not already described in the emactuzumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of emactuzumab. An unexpected adverse event is one that is not already described in the emactuzumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

M.D. Anderson will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations. Any required development safety update reports for the study will be handled by M.D. Anderson and submitted to regulatory authorities and ethics committees of the concerned participating sites, where applicable. The Principal Investigator will provide Genentech with the safety information provided for any development safety update report as soon as reasonably possible after completion.

Genentech agrees to forward to M.D. Anderson an executive summary of the Genentech Development Safety Update Report (DSUR) upon request from M.D. Anderson**.** Furthermore, Genentech agrees that M.D. Anderson may cross-reference the executive summary of the Genentech DSUR, as applicable.

Genentech will provide M.D. Anderson with amendments to the Investigator's Brochure or the applicable Reference Safety Information generated for the Emactuzumab product.

7.2.4 Pregnancy

A female patient must be instructed to stop taking the study drug and immediately inform the investigator if she becomes pregnant during the study. All participating sites should report all pregnancies within 24 hours to Genentech. The investigator should counsel the patient, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Pregnancies occurring up to 30 days after the completion of the study drug must also be reported to the investigator. Monitoring of the female patient should continue until conclusion of the pregnancy or until adequate due diligence with regard to obtaining follow-up information.

M. D. Anderson will be responsible for collecting, tracking and evaluating pregnancy reports where the patient has been exposed to the investigational product. Pregnancy reports will be sent on a MDACC SAE Reporting Form to the Genentech contact listed below. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within 24 hours of the awareness date.

Genentech
Genentech Drug Safety at: (650)-225-4682 OR (650)-225-4630. Please use the "Genentech Safety Reporting Fax Cover Sheet" provided at the end of the protocol.

Emactuzumab Safety at: new_york.ml29802predcontactsd@.roch.com

7.2.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the bevacizumab and emactuzumab Investigators' Brochure.

7.2.6 Safety Crisis Management

In case of a safety crisis, e.g. where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the investigational agents are used, or where there is media involvement, the participating site where the crisis originates will contact M.D. Anderson as soon as possible. M.D. Anderson will confirm details regarding safety issues with Genentech as soon as possible.

M.D. Anderson and Genentech and other participating sites (as appropriate) will discuss and coordinate any safety crisis issue; the overall principal investigator will have the final say and control over safety crisis management issues relating to the study with reasonable consideration of Genentech's comments. Any queries from media and other sources that are not regulatory authorities relating to the investigational agent used in the study (except for queries relating to MDACC's participation in the Study or a participating site's participation in the study) shall be discussed between MD Anderson's Communications Office and the Genentech contact listed below before any response is given.

Genentech

Genentech Drug Safety at: (650)-225-4682 OR (650)-225-4630. Please use the "Genentech Safety Reporting Fax Cover Sheet" provided at the end of the protocol.

Emactuzumab Safety at: new_york.ml29802predcontactsd@Genentech.com

7.2.7 Serious Adverse Event Reporting (SAE) for M. D. Anderson-sponsored Multicenter IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

Reporting for all sites:

- A written report should be submitted to the Institutional Review Board (IRB) according to the requirements of the assigned IRB for patients enrolled at each site. (The MD Anderson site will utilize the electronic SAE application (eSAE) for reporting SAEs.)
- SAEs will be reported to the sponsor on a template form that will be provided to each site. If needed, a copy of all relevant examinations that have been carried out and the dates on which these examinations were performed should be attached. For laboratory results, normal ranges should be included. Patient name should be marked out and initials and study number included on all attachments.

- In case of a serious adverse event, the following actions must be undertaken by the investigator: (Please note that these are *in addition* to reporting that is required by the local IRB and supporting company.) Complete the SAE form immediately and then fax and overnight mail the signed and dated SAE form to the sponsor representative **within two working days** to the following address:

  The University of Texas M.D. Anderson Cancer Center
  IND Office
  Attention: Dr. Agueda Cohen, Medical Monitor, IND Office
  7007 Bertner, 1MC12.2225
  Houston, Texas 77030
  Tel no.: 713-563-5466
  Fax no.: 713-792-8987
  e-mail: mdaccsafetyreports@mdanderson.org

  A copy of the tracking receipt should be kept and filed in the study regulatory binder at the site. The research team may e-mail or call the sponsor to confirm receipt of the SAE fax or mailed form.

- ***Death or life-threatening events that are possibly, probably or definitely related to drug must be reported within 24 hours***. The sponsor IND safety coordinator must be notified by phone immediately, in addition to fax or overnight mail as listed above.

- **All life-threatening or fatal events,** expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, unless the protocol states otherwise, and be reported until 30 days after the last**

dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**
- **All events reported the supporting company must also be report to the IND Office.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.2.8 Study Monitoring

The University of Texas MD Anderson Cancer Center IND Office will monitor the study investigators to assure satisfactory enrollment rate, data recording, and protocol adherence. The site principal investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. MD Anderson Cancer Center will monitor and/or audit the other participating sites to assure satisfactory protocol adherence and enrollment. The site will be visited on a regular basis by the Clinical Study Monitor, who will check completed source documentation, discuss the progress of the study and monitor drug according to good clinical practice (GCP). The monitoring will also include source data verification (SDV).

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Safety Decision Rule for Lead in: Part 1

Part 1 participants will be treated with the triplet combination of paclitaxel plus bevacizumab plus Emactuzumab. The primary endpoint is safety defined as no required dose alterations during the first cycle (4 wks) of therapy due to a Dose Limiting Toxicity (DLT). A dose limiting toxicity for this trial is defined as any Grade 4 hematologic toxicity including Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with bleeding, Grade 4 neutropenia persisting > seven days, febrile neutropenia, or Grade 4 anemia. A dose limiting toxicity is also defined as grade 3 or greater non-hematologic toxicity including laboratory abnormalities, however, for patients receiving Emactuzumab, any laboratory parameters that may be increased due to decreased clearance in the liver, for example, but not limited to, CK, LDH and transaminases (ALT/AST; see section 6.3.9.2.2 for details on expected asymptomatic decreases in hepatic clearance), if not associated with clinical signs and symptoms, will not be considered a dose limiting toxicity and also do not require expedited reporting as SAE's. See section 6.3.9 Dose Modifications and Table 7 for further guidance on managing toxicities related to Hepatic lab values. Close monitoring of liver function parameters (e.g. bilirubin elevation) is required to ensure that

the asymptomatic increases in LFTs due to emactuzumab are not masking signs of true liver damages due to other reasons. If Total Bilirubin is elevated to 2.0 xUNL in combination with elevated ALT/AST the criteria for Hy's Law may be met. Refer to section 6.3.9.2.2 for management guidelines for hepatic events. A total of 9 evaluable patients will be enrolled. The following decision rule will be followed:

Number of Patients with DLT	Number of Patients at Current Dose		
	3	6	9
0	P	P	A
1	S	P	A
2	U	U	A
3	U	U	U

P = proceed to treat additional patients
S = stay at the current dose – treat 3 more patients
A = Acceptable to open enrollment beyond patient safety lead-in
U = the current dose is unacceptably toxic, halt all enrollment

*Exclude lab abnormalities that don't meet criteria for AE reporting and observed increases in liver enzymes (e.g., AST, ALT, CK, LDH) due to known emactuzumab PD effect. LFT increases should count as a DLT only if there is true evidence of toxicities (e.g., increase in bilirubin)

§ If 3 DLT's are observed before 9 patients are enrolled, recruitment will stop and a new cohort of up to 9 additional patients will enrolled at emactuzumab at a dose confirmed after discussion with Genentech on days 1 and 15 on a 28-day cycle. If 3 or more DLT's are observed at this level, a discussion with Genentech, will be undertaken to consider other dosing/schedule opportunities.

Investigations should be conducted to exclude alternate causes of the abnormal LFTs, e.g.progression of underlying disease, infections or other diseases affecting liver function, concomittant medication and nutrition. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-LKM, and anti-smooth muscle antibody tests should be evaluated if an autoimmune etiology is considered.

For patients with documented liver metastasis and elevated LFT results at baseline, further elevations of LFT results may not require dose interruptions if there are no progressive changes in the ALT and/or AST (less than a doubling) and if there are no progressive elevations in total bilirubin or INR. Regular monitoring of LFTs, bilirubin, coagulation parameters will be conducted throughout the study in accordance with the schedule of assessments.

Patients who, upon restarting study treatment after resolution, experience another dose delay due to elevations of LFTs with concomitant increase of bilirubin and/or abnormal coagulation parameters should permanently discontinue treatment.

Study treatment should be discontinued for life-threatening immune-related hepatic events.

8.1.1 Patient Enrollment to Safety Lead in: Part 1

To ensure patient safety, the first three patients will be enrolled staggered with one week between enrollments of each patient. All three patients must complete one cycle of triplet therapy prior to enrollment of any additional patients on Part 1 of the study. If no dose-limiting toxicities are observed, the remaining six patients may be enrolled simultaneously. If any dose-limiting toxicity occurs in one of the first three patients enrolled, three additional patients will be enrolled sequentially (one week apart) and observed for one cycle (four weeks) prior to enrollment of additional patients. If any dose-limiting toxicity occurs in two of the first three patients enrolled in Part 1, the enrollment on the trial will be suspended pending a revised protocol with a new dosing schedule. Additionally, if a dose-limiting toxicity occurs in a second patient, even if enrollment of six patients has not been reached, the trial will be placed on hold and will require an amended protocol with a new dosing schedule. If three or more of the first nine patients experience any of the dose-limiting toxicities, no additional patients will be enrolled and the clinical trial will be halted pending a revised protocol with new dose level(s)/schedule and updated information regarding all toxicities observed while using the prior dose/schedule.

8.2 Statistical Considerations for Part 2

8.2.1 Induction Therapy: Part 2A

The intent of the Part 2A is to produce a sample cohort of patients treated with paclitaxel and bevacizumab who achieve stable disease at the first assessment. Estimation of this sample was interpreted from the AURELIA trial (n=361), which recruited a cohort of 115 patients treated with paclitaxel, 60 of whom were randomized to additionally receive open label bevacizumab. The eligibility, dosing and schedule for this regimen are identical to the current trial (REDIRECT).

8.2.1.1 Estimation of Sample size: Part 2A

In the paclitaxel/bevacizumab cohort of AURELIA, approximately 15% of patients experienced an event of progression or toxicity at or before the first RECIST (v 1.0) evaluation. Conservatively, we would raise this estimate to 15% to account for expectations/difficulties with travel, etc. Although difficult to estimate, the proportion of patients experiencing objective response at 8 weeks was estimated at 25%. In the paclitaxel/bevacizumab cohort of the AURELIA trial, objective response was 53% with a median duration of chemotherapy at 6 cycles (IQR: 4-8 cycles). The time to response by assessment cycle (every 8 weeks) is not available or published upon which to make this estimate. However, conservative estimates on a sample size at Part 2A in order to produce 80 eligible patients for randomization (Part 2B) is 112.

8.2.2 Randomization Cohort: Part 2B

The primary efficacy variable will be PFS from the date of randomization, which will occur in CORe. A sample size of approximately 80 patients (40 randomized to each treatment arm) will yield 83% power with a 2-sided significance level of 0.20 to detect an increase in the PFS at 32 weeks post-randomization from 50% to 75% using a log-rank test. This calculation is based on nQuery Advisor. We choose the significance level of 0.2 because the objective of this phase II is proof of concept, rather than confirmative.

8.2.2.1 Estimation of Treatment Effect: Part 2B

In the AURELIA trial (paclitaxel/bevacizumab arm), using a landmark analysis from week 8, the proportion of all patients being progression-free at a subsequent 32 weeks was approximately 61%. This analysis considers all patients not progressing at week 8, including those with early response. In the current trial, we will only be randomizing those patients in whom stable disease is the best response at week 8. Since this is unknown from the prior AURELIA publications, we are conservatively estimating that the PFS at 32 weeks post randomization will be 50% for the control arm (paclitaxel/bevacizumab). Our goal is to evaluate an effect size of increasing this PFS from 50% to 75%. We assume that we will accrue all 80 patients in 100 weeks. The maximum study duration is expected to be 127 weeks, and we expect to observe a maximum of 50 PFS events (i.e., progressive disease or death).

8.2.2.2 Statistical Analyses: Part 2B

We will use descriptive statistics to summarize the demographic and clinical characteristics of patients in the 2 treatment arms. We will estimate PFS from randomization with the product-limit estimator of Kaplan and Meier for each treatment arm, and we will use the stratified log-rank test to compare the 2 treatment arms with respect to PFS. We will use stratified Cox proportional hazards regression to model PFS as a function of treatment arm and estimate the hazard ratio with a 95% confidence interval. We will similarly analyze overall survival. We will tabulate tumor response by treatment arm, and we will estimate the rate of response (CR, PR, and CR+PR) with 95% confidence intervals. We will tabulate adverse events by grade and relationship to study drug for each treatment arm.

8.2.2.2.1 Interim Analysis: Part 2B

We will use the methods of Lan and DeMets to perform an interim analysis for futility and for efficacy once we have observed 25 patients with a PFS event. We control the overall type I error rate of 0.2 and power of 80%. We choose to use this relative large type I error rate because this is a phase II proof-of-concept trial. We assume that the PFS at 32 weeks post-

randomization is 50% and 75% for control and experimental arms, respectively. The accrual rate is 80 patients in 100 weeks. The interim analysis for efficacy will employ an O'Brien-Fleming stopping boundary with a nominal significance level of 0.04. The interim stopping boundary for futility is a nominal significance level of 0.8678. The nominal significance level for the final analysis will be 0.188.

For Part 2A and Part 2B, the toxicity will be monitored based on the following Bayesian rule: stop enrolling patients if the Pr(DLT > 25% | data) > 0.9. That is, we will stop enrolling patients if the data indicate that there is more than 90% chance that the true DLT rate is higher than 25%. This decision rule gives the following stopping rule, assuming a Beta(0.1, 0.4) prior distribution for DLT rate,

Stop enrolling pts if [# of pts with DLT] / [# of pts evaluated] ≥ 3/5, 5/10, 8/20, 11/30, and 14/40.

In Part 2A, the first 40 patients will be monitored using the above rule. We do not provide a formal stopping rule after 40 patients because by that time there are enough data to confirm the safety of the drug. After the 40 patients, the safety procedure described in Section 7 will be used to monitor AE. In Part2B, the two treatment arms will be monitored independently using the above stopping rule. The following table shows the operating characteristics of the safety stopping rule:

TABLE 15: OPERATING CHARACTERISTICS OF SAFETY STOPPING RULE

	True DLT rate				
	0.1	0.2	0.3	0.4	0.5
Stopping probability	0.008	0.098	0.401	0.789	0.967
Average sample size	39.7	37.1	29.7	19.3	11.9

8.2.3 Secondary efficacy variables

The secondary efficacy variables are objective response rate, overall survival and safety/tolerability.

Progression-free Survival (PFS): PFS is defined as the time from the date of randomization to the first documented disease progression or death, whichever occurs first. Progression will be based on tumor assessment made by the investigators according to the RECIST criteria (for patients with measurable disease), and as per Appendix 1 (for those with non-measurable disease). Patients who had not experienced an event at the data cut-off date or patients who are withdrawn from the study without documented progression will be censored at the date of the last tumor assessment when the patient was known to be progression free. Patients without post baseline tumor assessments but known to be alive will be censored at the time of the first study drug administration. The median PFS with 95% confidence interval and quartiles will be reported as well as Kaplan-Meier curves.

Objective response rate: ORR is determined as the rate of patients with an observed tumor response. ORR will be evaluated for three types of responders:

1. Patients who have a response as defined per RECIST and as defined using the 50% response criteria for CA-125 ("responders")
2. Patients who have a response as defined per RECIST but no response as defined using the 50% response criteria for CA-125 ("RECIST responders")
3. Patients who do not have a response as defined per RECIST but who do have a response as defined using the 50% response criteria for CA-125 ("CA-125 responders")

A detailed explanation regarding responder criteria is given in Appendix 1. Patients with no tumor assessment after the start of study treatment are to be considered as non-responders. The point estimate per treatment arm and the 95% Pearson-Clopper confidence interval for the objective response rates will be provided. Logistic regression analyses will be performed to assess the influence of baseline covariates in an exploratory manner. More details will be defined in the statistical analysis plan.

Biological progression-free interval: PFI_{bio} is defined on the basis of a progressive serial elevation of serum CA-125 at the time from the date of randomization to first documented increase in CA-125 levels to:

1. two times the ULN (for patients with normal pre-treatment CA-125 or elevated pre-treatment CA-125 and initial normalization on-treatment) or
2. two times the nadir value (for patients with elevated baseline CA-125 that did not normalize on-treatment).

In patients with radiologically measurable disease according to RECIST[61], progression during protocol treatment cannot be declared on the basis of CA-125 alone.

Overall survival: This is defined as the time from the date of Part 1 commencement or date of randomization (Part 2B) for up to 5 years. Patients who were alive at the time of the analysis will be censored at the date of their last follow-up assessment. Patients without follow-up assessment will be censored at the day of their last dose and patients with no post baseline information will be censored at the time of their first study drug administration.
The survival distribution will be summarized by Kaplan-Meier method. Medians of the overall survival as well as the associated 95% confidence intervals and quartiles will be provided per treatment arm. Kaplan-Meier curves will be used to graphically describe the observed distribution.
All tests will be performed at a two-sided 5% alpha level. No adjustments for multiplicity will be made during the analysis of secondary variables.

8.2.3.1 Analyses of Biomarkers: Part 2B

To fully assess the utility of surrogate biomarkers and the anti-tumor response to therapy with the combination treatment of bevacizumab and emactuzumab, we will draw 20 ml blood for plasma markers (VEGF, VEGFR, IL6, IL8, FGF, PDGFAA, CSF1, and IL34) and other chemokines identified by secretome proteomics) and potential exosomal markers (M2-like markers VEGFR1-3, CD11b +CD68, CD11b+CD14/CD15/CD33, CD11b+CD11c, MHCII), prior to initiation of paclitaxel/bevacizumab/emactuzumab and after pre-infusion every 4 weeks for the patient safety lead-in (Part 1), and randomized therapy (Part 2B). All PD blood draws are mandatory. In Part 2A, there will be one mandatory pre-treatment biopsy, and one optional biopsy at progression. In the Part 2B, we will seek to obtain 2 biopsies, one at pre-treatment tissue biopsy prior to initiation of bevacizumab (Part 2A portion) and one pre-randomization tissue biopsy following 4 weeks from last dose of bevacizumab (at preinfusion of emactuzumab), and optionally at progression. These biopsied tissues will be used for monitoring dynamic changes in adapted macrophages (with phenotype of M2-like: VEGFR1-

3+, CD markers (e.g. +CD68, CD163+), CSF1/CSF1R+ and MHCII^{low}), and hypoxia markers as well as CD4/CD8, NK, and T-reg. Please refer to schedule of events designated in Tables 1-4.

8.2.4 Safety variables

General physical examination, measurement of vital signs, laboratory safety assessments (as per local standard of care) and recording of AEs/SAEs will be completed at each study visit.
Clinical safety assessments will also include medical history, prior treatments for cancer and ECOG performance status.
Clinical and laboratory adverse events will be reported and graded according to NCI-CTCAE version 4.03. Safety of the treatment in both arms will be evaluated by the frequency of adverse events, laboratory tests, vital signs, and ECOG performance status during the study.

8.2.5 Analysis populations

The following population definitions will be used to analyze selected endpoints according using the appropriate subpopulation of the enrolled patients. If the need arises, additional subpopulations can be defined in the statistical analysis plan.

8.2.5.1 Safety analysis population

The Safety Population comprises all study patients who received at least one dose of any study medication. The safety population will be used for the analysis of all safety parameters. Patients are assigned to the treatment groups based on what they actually received.

8.2.5.2 Efficacy analysis population(s)

All patients who were randomized to one of the two treatment arms will be included in the Intent-to-treat (ITT) population and presented according to the therapy they were randomized to receive.
The Per Protocol (PP) population is defined as the subset of ITT population who have received at least one study treatment cycle and had no major violation of the protocol inclusion and exclusion criteria.
All efficacy analyses will be based on the ITT population. The primary and secondary efficacy analyses will be repeated using the PP population to confirm the overall study results.

8.2.6 Safety data analysis

All safety parameters will be summarized and presented in tables based on the safety population described in section 8.2.5.1.
All adverse events and abnormal laboratory variables will be assessed according to the CTCAE v4.03 grading system. However, only Grade 2-5 events will be captured in the eCRF and clinical database. Grade 2-5 adverse events and separately, serious adverse events, will be presented in frequency tables (overall, by intensity and by relationship to study treatment) by body system and preferred term, using a current MedDRA dictionary. The number of patients with any grade 2-5 adverse events and the number of patients with an adverse event of special interest will be presented together with 95% Pearson-Clopper confidence intervals. In addition, the number of events (grade 2-5 adverse events, serious adverse events, and adverse events of special interest) per patient year under treatment will be calculated and descriptively presented.

Selected events of particular interest (e.g. GI perforation) will be presented in summary tables. The time to first onset of the event and the total number of episodes will be presented. Every occurrence of an event in any patient will be counted in the total number of episodes but successive reports of an identical event in the same Phase (treatment, follow-up) will be combined (concatenated) into one episode if the end date of the earlier event was the same as the start date of the later event, or if the end date of the earlier event was missing.
Descriptive statistics will be used to summarize ECOG performance status. Vital signs, electrocardiograms, and neurological examinations will be reported in tables or listings, as appropriate.
Treatment exposure will be summarized as the number of cycles received by each patient, the time from first to last treatment, and as the percentage of the planned dose of each agent given at each cycle.

8.2.6.1 Toxicity and Efficacy Reporting to MDACC IND Office

The Investigator is responsible for completing toxicity and efficacy summary reports, and submitting them to the IND Office Medical Affairs and Safety Group, for review. These should be submitted as follows:

- Part 1:
  A Toxicity Summary report, after the first 3 evaluable subjects, complete cycle 1 of triplet therapy, and every 3 evaluable subjects thereafter, prior to changing dose levels or advancing to Part 2A.

- Part 2A:
  A Toxicity/Efficacy Summary report, after the first 5 evaluable subjects, complete cycle 1 of study treatment, and every 10 subjects thereafter, until the 40th evaluable patient. On every summary submission, prior subjects' reported best response will need to be updated.

- Part 2B:

An Efficacy/Toxicity summary report, after the first 5 evaluable subjects per arm, complete cycle 1 of study treatment, and every 10 subjects thereafter, until enrollment is complete. On every report submission, prior subjects' best response will need to be updated.

9. DATA QUALITY ASSURANCE

9.1 Data collection

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

All data will be entered into the Prometheus Software Platform. Prometheus is a secure portal that requires users to login with validated credentials, has granular data access controls to ensure that the minimal amount of information required to complete a task is presented, handles the de-linking and de-identification of patient information to maintain patient confidentiality. Prometheus provides a multi-institute 21 CFR 11 compliant data capture portal to simplify these tasks. Standard data collection, storage procedures, and quality assurance procedures will be followed to ensure integrity and auditability of all

information entered. Accurate and reliable data collection will be assured by verification and cross–checking of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug–dispensing log by the investigator. Oversight of the MD Anderson Cancer Network sites will be handled through the Clinical Research Support Center utilizing the M.D. Anderson institutional SOPs that are in place. Monitoring of all sites will be handled by the M.D. Anderson IND office.

9.2 Data management

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the Prometheus database will verify the data and discrepancies will be generated accordingly. These are transferred electronically to the eCRF at the site for resolution by the investigator.

Queries related to the study at M.D Anderson will be answered by M.D Anderson. Queries directed to a participating site's participation in the study will be coordinated with MD Anderson and answered by the participating site, this includes all safety queries from regulatory authorities or for publications. M.D Anderson and Genentech agree that MD Anderson shall have the final say and control over safety queries relating to the study at M.D Anderson (or the participating site, as applicable).

MD Anderson and Genentech and any participating site, as applicable, will use reasonable efforts to ensure that deadlines for responses to urgent requests for information or review of data are met. MD Anderson and Genentech and any participating site, as applicable will clearly indicate on the request the reason for urgency and the date by which a response is required; provided, however, that no such coordination effort will impair MD Anderson's (or the participating site, as applicable) ability to timely respond to such query.

MD Anderson Cancer Center will forward a copy of the Final Study Report and the Final IND Annual Report to Genentech upon completion of the Study.

9.3 Study Close Out

MD Anderson Cancer Center will forward a copy of the Final Study Report and the Final IND Annual Report to Genentech upon completion of the Study.
Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study, see section 16.6.

9.4 Assignment of preferred terms

For classification purposes, preferred terms will be assigned by the sponsor to the original terms entered on the eCRF, using the current version of MedDRA (medical dictionary for regulatory activities) for AEs and diseases and the INN (international non-proprietary name) drug terms and procedures dictionary for treatments and surgical and medical procedures.

9.5 Study committees

A Data Safety Monitoring Board (DSMB) at M.D. Anderson reviews the protocol annually or if necessary at other times determined by the chair. The DSMB Chair or a designated member will notify the study team with a follow up memo following each DSMB committee review.

The DSMB will be responsible for independently evaluating the safety of the patients participating in the trial. Specifically, the DSMB will review and evaluate the safety data emerging from each cohort. If the DSMB has safety concerns regarding one of the treatment cohorts, the DSMB may recommend to close recruitment into that cohort. The implementation of such recommendation will disallow the data from the final primary analysis, however, these data will still be analyzed and reported in descriptive terms.

10. ETHICAL ASPECTS

10.1 Local regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient.

10.2 Informed consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. Patients who cannot make an unbiased decision or patients who are institutionalized due to regulatory or judicial order are not allowed to participate. For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The eCRFs for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients [including those already being treated] should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

In a life-threatening situation where a patient is unconscious or otherwise unable to communicate, the emergency is such that there is not enough time to obtain consent from the patient's legally acceptable representative, and there is no other or better treatment available, it is permissible to treat the patient under protocol with consent of the investigator, with appropriate documentation that the IRB had approved the procedures used to enroll patients in such situations. In addition, the patient or his/her legally acceptable representative should be informed about the trial as soon as possible and consent to continue, giving written consent as described above.

10.3 Independent Ethics Committees

This protocol and any accompanying material provided to the patient (such as patient information sheets or descriptions of the study used to obtain informed consent) as well as any advertising or compensation given to the patient, will be submitted by the investigator to the IRB.

Approval from the committee must be obtained before starting the study, and should be documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the IRB approval must also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

11. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the sponsor and the investigator representative(s). Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the PI and Biostatistician.

All protocol modifications must be submitted to the appropriate IRB for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s).

12. CONDITIONS FOR TERMINATING THE STUDY

Both Genentech and M.D. Anderson reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Genentech and the Sponsor/investigator will ensure that adequate consideration is given to the protection of the patient's interests.

13. STUDY DOCUMENTATION, ECRFS AND RECORD KEEPING

13.1 Investigator's files / retention of documents

The Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different separate categories [1] Investigator's Study File, and [2] patient clinical source documents.

The investigator's study file will contain the protocol/amendments, independent ethics committee and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents, correspondence etc.

The Investigator will keep the Study File and patient clinical source documents (including MRI/CT scans) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, Genentech must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Genentech to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

13.2 Source documents and background data

Patient clinical source documents shall include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, CT/MRI, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrollment logs. In no case is the eCRF to be considered as source data for this trial.

The investigator shall supply Genentech, on request, any required background data from the study documentation or clinic records. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

13.3 Audits and inspections

The investigator should understand that source documents for this trial should be made available to health authority inspectors after appropriate notification.

13.4 Case Report Forms

For each patient enrolled, an eCRF will be completed and signed by the principal investigator or authorized delegate from the study staff. For those patients who fail screening, only an ESF Form will be completed. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and in all required reports.

14. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator must ensure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrollment log showing codes, names and addresses. The investigator should maintain documents not for submission to Genentech, e.g., patients' written consent forms, in strict confidence, at the site.

15. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Genentech prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accord with standard editorial and ethical practice, Genentech will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which input of Genentech personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Genentech personnel. Authorship will be determined by mutual agreement.

16. APPENDICES

16.1 Appendix 1 Evaluation of Residual Disease, Evaluation of and Definitions of Response and Progression

16.1.1 Tumor Imaging and Assessment of Disease (RECIST v1.1)

Physical examination

• Lesions detected by physical examination will only be considered measurable if superficial, e.g., skin nodules and palpable lymph nodes. Documentation by color photography including ruler is recommended for estimating the size of skin lesions.

CT scan with contrast of the chest, abdomen, and pelvis

• CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

MRI scans

• MRI of the abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

16.1.2 Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- Measurable Lesions - Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- Nonmeasurable Lesions - Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- Target Lesions - All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- Non-target Lesions - It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

16.1.3 Response Criteria

16.1.3.1 Evaluation of Target Lesions

- Complete Response - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be “0” if there are target nodes).
- Partial Response - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- Stable Disease - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

16.1.3.2 Evaluation of Non-target Lesions

- Complete Response - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-complete response/Non-progressive disease - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from ‘trace’ to ‘large,’ an increase in lymphangitic disease from localized to widespread.

16.1.3.3 Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v 1.1 guidelines. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive emactuzumab if investigators consider that subjects continue to benefit from treatment.

16.1.3.4 Evaluation of Overall Response with Modifications

Confirmation of CR, PR, as well as PD is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. Treatment with emactuzumab will continue between the initial assessment of PD and confirmation for PD.
Tables 16 and 17 provide overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

TABLE 16. EVALUATION OF OVERALL RESPONSE

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non-target lesion)	No	Complete response
No target lesion at baseline	Complete response	No	Complete response
Complete response	Not evaluable	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable (or no non-target lesion)	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion)	No	Stable disease

TABLE 17. EVALUATION OF OVERALL RESPONSE

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion	Not all evaluated	No	Not evaluable
No target lesion	Non-complete response / non-progressive disease	No	Non-complete response / non-progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion	Any	Yes	Progressive disease

16.1.3.5 MRI Scans

Specific lesions must be evaluated serially, and comparative analysis of changes in the area of contrast enhancement, as well as the nonenhancing component, should be performed. The product of the maximal cross-sectional enhancing diameters will be used to determine the size of the contrast-enhancing lesions.

Minimum sequences required:

- Pre-contrast T1, T2/ fluid attenuated inversion recovery (FLAIR)
- Post-contrast T1, with two orthogonal planes (or a volume acquisition) recommended

- Recommended slice thickness ≤ 5 mm with no gap

16.1.4 CA-125 responses

Guidelines for using CA-125 response have been developed. Please refer to http://www.gcig.igcs.org/CA-125.html. Patients should have a pre-treatment CA-125 of at least twice the ULN in order to be considered for CA-125 response. Patients are not evaluable by CA 125 if they have received mouse antibodies or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. In those patients, a CA-125 response would be obtained the moment the CA-125 is reduced by 50% and this should be confirmed with a consecutive CA-125 assessment not earlier than 28 days after the previous one, with however the date of the first 50% reduction to be the reference date for the CA-125 response.

16.1.4.1 PROGRESSION OR RECURRENCE BASED ON SERUM CA-125 LEVELS

Biological Progression Free Interval (PFI_{BIO}) will be defined on the basis of a progressive serial elevation of serum CA-125 according to the following criteria:

In patients with radiologically measurable disease, progression during protocol treatment cannot be declared on the basis of CA-125 alone.

Patients with elevated CA-125 pre-treatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart or

Patients with elevated CA-125 pre-treatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart or

Patients with CA-125 in the normal range pre-treatment must show evidence of CA 125 greater than or equal to two times the upper normal limit on two occasions at least one week apart.

Elevated values must be confirmed by two separate measurements obtained at least one week apart. PFI_{BIO} will be assigned the date of the first measurement that meets the criteria as noted.

16.2 Appendix 2 - ECOG Performance Status Scale

- Description	- Scale
- Normal activity	- 0
- Symptomatic but ambulatory self-care	- 1
- Ambulatory more than 50% of the time	- 2
- Ambulatory 50% or less of time, nursing care needed	- 3
- Bedridden, may need hospitalization	- 4
- Death	- 5

16.3 Appendix 3 – ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms
If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths
All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions
A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:
- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

A SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. An SAE is any AE that at any dose fulfils at least one of the following criteria:

- is fatal; (results in death) [NOTE: death is an outcome, not an event]
- is life-threatening [NOTE: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe]
- required in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For SAEs, possible causes of the event are indicated by selecting one or more options (check all that apply).

- Pre-existing/Underlying disease - specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g. accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A SAE occurring during the study or within 15 days after stopping the treatment, or during the protocol-defined follow-up period must be reported. In addition, a SAE that occurs after this time, if considered related to the study drug should also be reported.

Such preliminary reports will be followed by detailed descriptions which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For SAEs, the following must be assessed and recorded on the AEs page of the CRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Review Committee/Institutional Review Board of a SAE in writing as soon as is practical and in accordance with international and local laws and regulations.

GENENTECH LOCAL COUNTRY CONTACT for SAEs: Local Monitor

GENENTECH HEADQUARTERS CONTACT for SAEs: Clinical Operations/Clinical Science

16.3.1 MD Anderson Cancer Center SAE Reporting Guidelines

MDACC SAE form Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description of the MDACC SAE form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MDACC SAEreport and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MDACC SAEform
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

16.4 Appendix 4: NEW YORK HEART ASSOCIATION (NYHA) GUIDELINES

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

16.5 Appendix 5: PROCEDURE FOR OBTAINING A URINE PROTEIN:

Procedure for Obtaining a Urine Protein / Creatinine Ratio

1) Obtain at least 4 ml of a random urine sample (does not have to be a 24 hour urine)
2) Determine protein concentration (mg/dL)
3) Determine creatinine concentration (mg/dL)
4) Divide #2 by #3 above: urine protein / creatinine ratio = protein concentration (mg /dL) / creatinine concentration (mg /dL)

The UPC directly correlates with the amount of protein excreted in the urine per 24 hrs (i.e. a UPC of 1 should be equivalent to 1g protein in a 24hr urine collection)

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.

16.6 Appendix 6- Genentech Contacts

GENENTECH CONTACTS

Activity	Person Responsible
Clinical Operations Contact	Dianne Tuccillo Clinical Study Manager P: 781-859-5413 E: tuccillo.dianne@gene.com
General Queries/Aggregate Reports	**To:** Drug Safety Contact Line Mailbox: contact_line.drug_safety@roche.com Tel: + 41 61 68 78841
Single Case Management	**Single Case Reports To Genentech:** Central Operations Mailbox: welwyn.pds-pc@roche.com Fax (Clinical): +44 1707 377 967/ 373 779/ 373 793/ 390 959 Fax (Spontaneous): +44 1707 390 904 **Queries on Single Case Reports/Reconciliation:** Regional Center Europe (RCE) mailbox: welwyn.contact_line_rce@roche.com **CC: Avastin** Katherine Y. Look M.D. Senior Medical Director - Avastin Medical Affairs/GYN Genentech BioOncology P: 650-225-7832 E: look.katherine@gene.com **CC: Emactuzumab** Dominik Rüttinger, M.D., Ph.D. Translational Medicine Leader - Genentech Pharmaceutical Research and Early Development (pRED) Innovation Center Penzberg P: +49 8856 60 19705 E: new_york.ml29802predcontactsd@Genentech.com
Safety Crisis Management Final Study Report SDEA	**Avastin** Katherine Y. Look M.D. Senior Medical Director - Avastin Medical Affairs/GYN Genentech BioOncology P: 650-225-7832 E: look.katherine@gene.com **Emactuzumab** Dominik Rüttinger, M.D., Ph.D. Translational Medicine Leader - Genentech Pharmaceutical Research and Early Development (pRED) Innovation Center Penzberg P: +49 8856 60 19705 E: new_york.ml29802predcontactsd@Genentech.com
IB updates for Emactuzumab	**Emactuzumab** Dominik Rüttinger, M.D., Ph.D. Translational Medicine Leader - Genentech Pharmaceutical Research and Early Development (pRED) Innovation Center Penzberg P: +49 8856 60 19705 E: new_york.ml29802predcontactsd@Genentech.com

16.7 Appendix 7- Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET
Genentech Supported Research

AE / SAE FAX No: (650) 225-4682
Alternate Fax No: (650) 225-4630

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[INSERT investigational product name] / [INSERT investigational product name] / [INSERT investigational product name]
Follow-up Report Date	[INSERT investigational product name] / [INSERT investigational product name] / [INSERT investigational product name]

Subject Initials (Enter a dash if patient has no middle name)	[INSERT investigational product name] - [INSERT investigational product name] - [INSERT investigational product name]

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

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