NCT01767857

Trial Protocol

A Phase III Double-blinded, Placebo Controlled Study of Xilonix™ for Improving Survival in Metastatic Colorectal Cancer

SPONSOR

XBiotech USA Inc

05 June 2017

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Basic Information

STUDY TITLE: Phase III Double-blinded, Placebo Controlled Study of Xilonix™ for Improving Survival in Metastatic Colorectal Cancer

INVESTIGATIONAL PRODUCT:	Xilonix™
IND Number	114,759
PROTOCOL NUMBER:	**2012-PT023**
PROTOCOL VERSION / DATE:	Version 3.7 / June 5th, 2017
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Investigator/Sponsor Signatures

STUDY TITLE: Phase III Double-blinded, Placebo Controlled Study of Xilonix™ for Improving Survival in Metastatic Colorectal Cancer

STUDY PRINCIPAL INVESTIGATOR SIGNATURE:

I have read the protocol and appendices. I understand the contents and intend to comply fully with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal authorization by XBiotech USA, Inc., in the form of a protocol amendment.

INVESTIGATOR SIGNATURE:

_____

Printed name of Investigator

_____

Signature

_____

Date

SPONSOR SIGNATURE:

XBiotech USA, Inc.

Michael Stecher M.D., Medical Director

_____

Signature

_____

Date

Clinical Protocol Synopsis

Study Title:

Phase III Double-blinded, Placebo Controlled Study of Xilonix™ for Improving Survival in Metastatic Colorectal Cancer

Sponsor:

XBiotech USA, Inc.

Study Chair:

George Fisher M.D., Ph.D.

Sample Size:

Approximately 600 subjects.

Approximate Duration:

The total study duration is 18 months. The duration of subject participation in the evaluation of body composition is approximately 77 days (including a screening period of 14 days and a treatment/follow up period of 63 days). Subjects with radiographic evidence of progression, as assessed by the Immune Related Response Criteria (irRC) should be discontinued from therapy.

Study Objectives:

Primary Efficacy Endpoint

- Overall survival (OS) will be the primary endpoint of this study, which will be measured from the date of randomization until death or last follow-up.

Secondary Efficacy Endpoints

- Secondary efficacy variables will include change in lean body mass (LBM) measured by dual-energy X-ray absorptiometry (DEXA) scans, change in Quality of Life assessed through the cancer-specific EORTC QLQ-C30 questionnaire, stabilization of platelet counts, progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR).

Study Rationale:

In the setting of refractory, metastatic disease a complete resolution of tumor burden is not a reasonable expectation. Instead, the primary goal of anti-tumor therapy at this stage is to eliminate or reduce the symptomatic effects of the tumor, while trying to prolong survival for as long as possible. Due to treatment related morbidity however, few treatment modalities are ideal for this objective. Even with the most recent targeted agents (such as multi-kinase inhibitors), drug related toxicities frequently lead to relatively short treatment durations. With discontinuation of therapy, disease progression is uncontrolled and prognosis is poor.

New agents that control disease progression—while improving tumor-related symptoms, rather than causing significant therapy related morbidity—are vitally needed to treat patients with advanced cancer, including those with colorectal cancer. An approach has been taken to develop such an agent using a monoclonal antibody to block the chronic inflammation involved in both malignant disease progression and constitutional symptoms.

Xilonix™ is expected to inhibit tumor growth and metastasis by interrupting crucial signals that drive angiogenesis and invasiveness. The antibody therapy may also block tumor microenvironment infiltration by leukocytes (such as myeloid suppressor cells) that suppress antitumor immunity, enabling better host immune control of the disease. In addition to local effects on the tumor, Xilonix™ is expected to work systemically to correct the metabolic dysregulation, fatigue and anxiety mediated by chronic inflammatory signaling to the central nervous system.

We have reported the first observation that increases in lean body mass (LBM) in patients with advanced metastatic disease are associated with a very substantial survival benefit. In the recent clinical study where these observations were made, patients were treated with an anti-IL-1α therapeutic antibody (Xilonix™) to block tumor-related inflammation. Dual energy X-ray absorptiometry was used to accurately and objectively measure changes in body mass, and discriminate between changes in lean mass (i.e. muscle) and fat. LBM increased an average of 1.9±2kg within 8 weeks in 70% of the per-protocol population ($p<0.001$). In the colorectal carcinoma cohort, patients that gained lean body mass had dramatic improvement in survival (19.3 months vs 6.6 $p=0.098$) compared to those that lost lean mass[1].

Dramatic improvement in survival in patients with increasing LBM after treatment with an anti-IL-1α therapeutic antibody suggests new hope for treating patents that are currently considered refractory. The use of this antibody monotherapy to target chronic inflammation is proposed as a safe, effective treatment for patients with metastatic colorectal cancer.

Trial Design:

This is a phase III, multicenter, double blind, randomized, placebo controlled pivotal trial of the True Human monoclonal antibody MABp1 (Xilonix™) in subjects with metastatic colorectal cancer who are refractory to standard therapy.

- Enrolled subjects will be randomized (2:1) to receive either MABp1 plus best supportive care (BSC) versus placebo plus BSC.
- BSC is defined as those measures intended to provide palliation of symptoms and improve quality of life. This includes, but is not limited to, antibiotics, anti-emetics, narcotics, and parenteral nutrition.

- Subjects randomized to MABp1 or placebo will receive 7.5 mg/kg of study drug via intravenous infusion once every 2 weeks (one cycle).
- Study drug will be administered under close observation in a facility equipped to handle medical emergencies. Subjects must be observed for at least 1 hour with stable vital signs following the end of the infusion.
- Efficacy will be assessed by comparing overall survival (OS) between the MABp1 and placebo groups.
- Secondary endpoints will include change in lean body mass and quality of life from screening to the cycle 5 assessment. Other secondary endpoints will be progression-free survival, objective response rate (ORR), disease control rate (DCR), and stabilization of platelet counts. Lean body mass measurements will be obtained through the use of dual-energy X-ray absorptiometry (DEXA) scans. Quality of life will be assessed with the EORTC QLQ-C30 (v. 3). Response and progression will be evaluated using the Immune Related Response Criteria (irRC).
- Safety assessments will include physical examinations, vital signs, standard clinical laboratory evaluations (blood chemistry, urinalysis, and hematology), allergic reaction monitoring and adverse event monitoring.
- Pharmacokinetics samples will be taken in all patients. The pharmacokinetics of MABp1 in plasma will be randomly analyzed. Plasma samples will also be randomly monitored for the development of anti-MABp1 antibodies. If the study meets the primary endpoint, then all samples will be tested.

Inclusion Criteria:

No waivers/exemptions will be granted for protocol inclusion/exclusion criteria.

Subjects are included in the study if they meet all of the following criteria:

1. Subjects with pathologically confirmed colorectal carcinoma that is metastatic or unresectable and which is refractory to standard therapy. To be considered refractory, a subject must have experienced progression (or intolerance) after treatment with at least all of the following agents: oxaliplatin, irinotecan, flouropyrimidine, and cetuximab or panitumumab if KRAS wildtype.
2. Subjects will not be treated with any radiation, chemotherapy, or investigational agents while enrolled in this protocol.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
4. At least 2 weeks since the last previous cancer treatment including: chemotherapy, radiation therapy, immunotherapy, surgery, hormonal therapy, or targeted biologics and 4 weeks for patients who received treatment immediately prior to the study with anti-IL-1 or anti-TNF agents.
5. Age ≥ 18 years, male or female subjects.
6. Serum potassium and magnesium levels within Central Lab normal limits. Total serum calcium or ionized calcium level must be greater than or equal to the lower limit of normal. Subjects with low potassium, calcium and magnesium levels may be replenished to allow for protocol entry.
7. Adequate renal function, defined by serum creatinine ≤ 1.5 x Central Lab ULN.
8. Adequate hepatic function defined as:
    - total bilirubin ≤ 1.5 times the Central Lab ULN
    - alanine aminotransferase (ALT) ≤ 2.0 times the Central Lab ULN
      Exception: subjects with known liver metastases: ≤ 3.0 times the institutional ULN for ALT.
9. Adequate bone marrow function as defined as:
    - absolute neutrophil count (neutrophil and bands) of ≥ 1,500/mm^3 (≥ 1.5 x 10^9/L)
    - platelet count of ≥ 100,000/mm^3 (≥ 100 x10^9/L)
    - hemoglobin of ≥ 9 g/dL
10. For women of childbearing potential (WOCBP), a negative serum pregnancy test result at Screening and monthly thereafter.

For women who are not postmenopausal (24 months of amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to use adequate methods of contraception, during the treatment period and for at least 1 month after the last dose of study drug.

Acceptable contraceptive measures include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: Oral, Intravaginal or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation; Oral, injectable, implantable, intrauterine device (IUD), intrauterine hormone-releasing system(IUS)
- Barrier or sterilization methods such as condoms, bilateral tubal occlusion, vasectomized partner or sexual abstinence

For men: agreement to use a barrier method of contraception during the treatment period and for at least 1 month after the last dose of study drug

11. Signed and dated institutional review board (IRB)-approved informed consent before any protocol-specific screening procedures are performed.
12. Patients enrolled must, in the Investigator's judgment, be healthy enough to stay on the clinical trial for three months.

Exclusion Criteria:

Subjects with ANY of the following will be excluded from the study:

1. Mechanical obstruction that would prevent adequate oral nutritional intake.
2. Serious uncontrolled medical disorder, or active infection, that would impair the ability of the patient to receive protocol therapy.
3. Uncontrolled or significant cardiovascular disease, including:
    - A myocardial infarction within the past 6 months.
    - Uncontrolled angina within the past 3 months.
- Congestive heart failure within the past 3 months, defined as New York Heart Association (NYHA) Classes II or higher.
    - Diagnosed or suspected congenital long QT syndrome.
    - Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, Wolff-Parkinson-White (WPW) syndrome, or torsade de pointes).
    - Any history of second or third degree heart block (may be eligible if currently have a pacemaker).
    - Uncontrolled hypertension (blood pressure >140 mm Hg systolic and >90 mm Hg diastolic).
4. Dementia or altered mental status that would prohibit the understanding or rendering of informed consent.
5. Subjects who have not recovered from the adverse effects of prior therapy at the time of enrollment to ≤ grade 1; excluding alopecia and grade 2 neuropathy.
6. Immunocompromised subjects, including subjects known to be infected with human immunodeficiency virus (HIV).
7. Known hepatitis B surface antigen and/or positive hepatitis C antibody and presence of hepatitis C RNA.
8. History of tuberculosis (latent or active) or known positive Interferon-gamma release assay (IGRA).
9. Receipt of a live (attenuated) vaccine within 1 month prior to Screening.
10. Subjects with history of hypersensitivity to compounds of similar chemical or biologic composition of Xilonix™.
11. Women who are pregnant or breastfeeding.
12. WOCBP or men whose sexual partners are WOCBP who are unwilling or unable to use an acceptable method of contraception for at least 1 month prior to study entry, for the duration of the study, and for at least 1 month after the last dose of study medication.
13. Weight loss >20% in the previous 6 months.
14. History of progressive multifocal leukoencephalopathy or other demyelinating disease
15. Subjects on immunosuppressive therapy, including transplant patients

Abbreviations

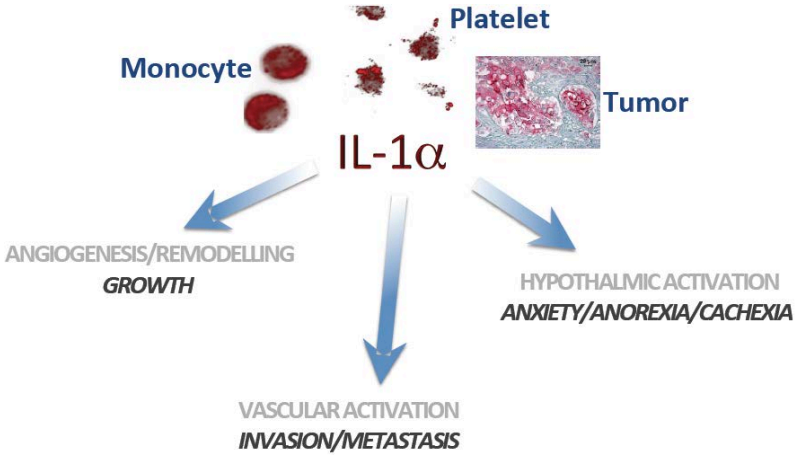
AE	Adverse event
ALT	Alanine aminotransferase (ALT, SGPT)
PT/aPTT	Prothrombin Time/Activated Partial Thromboplastin Time
ALP	Alkaline phosphate
BMI	Body Mass Index
BP	Blood pressure
CACS	Cancer Anorexia Cachexia Syndrome
CBC	Complete blood counts
CI	Confidence interval
CH	Heavy chain constant region
CL	Light chain constant region
eCRF	Electronic Case report form
CRA	Clinical Research Associate
CRP	C-reactive Protein
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP3A4	Cytochrome P450, 3A4 subfamily
DEXA	Dual Energy X-Ray Absorptiometry
EC	Ethics Committee
EKG	Electrocardiogram
EN	Expected Sample Size
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
EORTC-QLQ	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
IL-1 α	Interleukin-1 α
IL-1β	Interleukin-1 β
IL-1 RA	Interleukin-1 receptor antagonist
IL-1R1	Interleukin-1 Receptor 1
IL-1R2	Interleukin-1 Receptor 2
INR	International normalized ratio
IRB	Institutional review board
irRC	Immune Related Response Criteria
LBM	Lean Body Mass
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NSCLC	Non-Small Cell Lung Cancer
pI	Isoelectric Point
SAE	Serious Adverse Event
PK	Pharmacokinetics
PFS	Progression Free Survival
TNFα	Tumor necrosis factor α
TGFβ	Transforming growth factor β
TNF	Tumor necrosis factor
ULN	Upper limit of normal
WBRT	Whole brain radiation therapy
WOCBP	Women of childbearing potential

1. BACKGROUND

1.1 TARGETING INTERLEUKIN-1 ALPHA (IL-1α)

Specific antagonism of IL-1α through Xilonix™ therapy is viewed as a unique, broad acting tumor suppression strategy that encompasses significant activity to ameliorate symptoms associated with the disease. IL-1α is unique in its involvement in so many processes related to tumor progression and collateral symptomatic effects of malignancy. The excellent safety and tolerability profile of the agent make it an ideal treatment option in advanced stage disease, particularly where the use of cytotoxic or other therapies with considerable toxicity are not supported by the risk benefit profile.

Figure 1.1



IL-1α is expressed constitutively on monocytes and platelets and may be expressed by tumors. IL-1α activity promotes tumor growth and spread through multiple pathways.

In the setting of metastatic cancer, the loss of lean body mass is without doubt a prognostic factor for mortality, irrespective of underlying tumor type[2,3,4,5]. Multiple clinical investigations have shown that wasting predicts toxicity due to conventional chemotherapy, time to disease progression, and overall mortality in virtually all forms of cancer[6,7,8,9,10]. Loss of lean mass with advanced cancers thus represents a common final pathway amongst varied tumor types, which ultimately leads to death.

Blocking IL-1α appears to normalize the metabolic energy balance with the net accumulation of lean body mass (LBM). An average LBM increase of 1.9±2kg was seen in 70% of patients treated ($p<0.001$) compared to their baseline values. These same patients had improvements in pain, anorexia, and fatigue as measured by the EORTC-QLQ-C30. For the first time, a non-toxic, anti-neoplastic agent has shown evidence of the ability to reverse the devastating metabolic symptoms observed in advanced cancer patients. Even more impressive, however, was that increases in LBM also correlated with an increased overall survival.

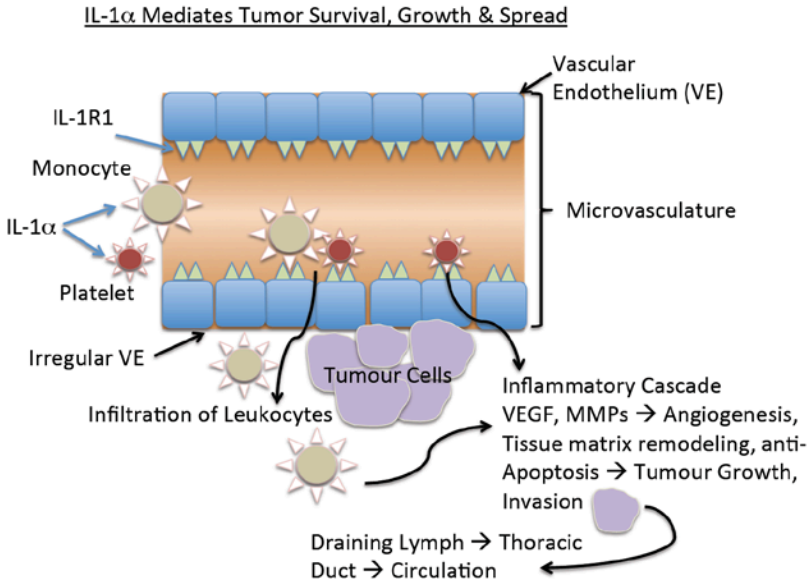
1.2 PLEIOTROPIC MECHANISM OF ACTION

There are over six-thousand published manuscripts on the science and physiology of IL-1α. The multitude of reports relate to the breadth and importance of this molecule in human physiology. Among these is its role in the growth, spread and collateral damage caused by tumors.

Neutralizing IL-1α activity with a monoclonal antibody therapy is believed to have broad antineoplastic activity. Depending on the site of action, IL-1α mediates a number of crucial physiological processes related to response to injury (e.g. tumor growth). At the site of injury (such as in the microenvironment of the growing tumor), IL-1α induces the expression of vascular growth factors including vascular endothelial growth factor (VEGF), thereby mediating growth and angiogenesis[11,12] (Figure 1.2). IL-1α also induces expression of matrix metalloproteinases that, in turn, have pleiotropic activities including tissue matrix breakdown, regulation of FAS mediated apoptosis and inflammation[13,14].

Through its role on platelets, IL-1α also regulates interactions between endothelial cells and leukocytes, driving activation of vascular endothelial cells and transendothelial migration of inflammatory cells into the tumor microenvironment[15]. Similarly, tumor-platelet microemboli formed between platelets and circulating tumor cells, provides tumor cells with enhanced ability to migrate from the vasculature into the tissues, forming new metastasis. Finally, IL-1α links these tumor processes to metabolic dysregulation, by signaling an injury response through IL-1 receptors on POMC neurons that interdigitate the endothelial microvasculature of the hypothalamus.

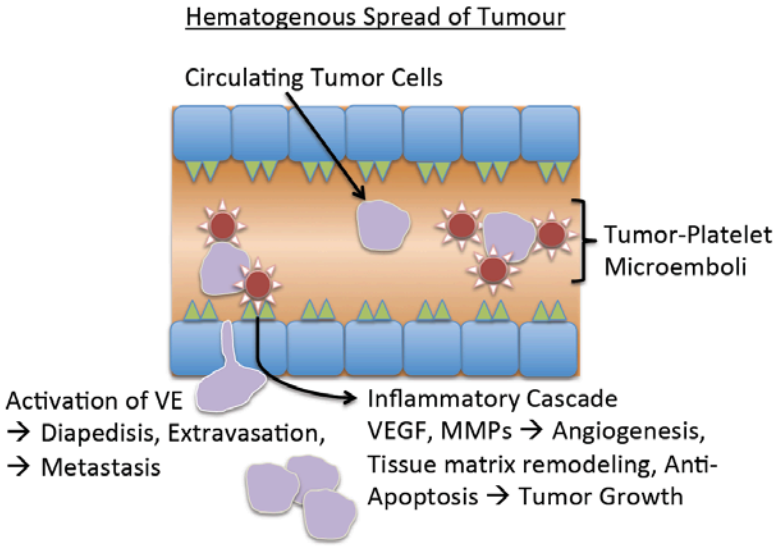
Figure 1.2: IL-1α Mediates Tumor Growth



Initial growth of tumor results in an irregular microvasculature leading to enhanced platelet interaction with vascular endothelial cells. IL-1α present on platelets and/or produced by tumor cells activates the endothelium, resulting in upregulation of adhesion molecules (ICAM, VCAM, E-selectin) and secretion of chemotactic cytokines (IL-8, MCP-1), facilitating diapedesis and recruitment of leukocytes into the tumor microenvironment[16,17,18]. IL-1α released from necrotic tissue and present on infiltrating tumor associated macrophages (TAMs) induce expression of MMPs, VEGF and other factors crucial to tumor survival, growth, and spread[19,20,21,22]. Additionally, TAMs suppress T-cell proliferation, allowing tumor cells to escape immune surveillance.

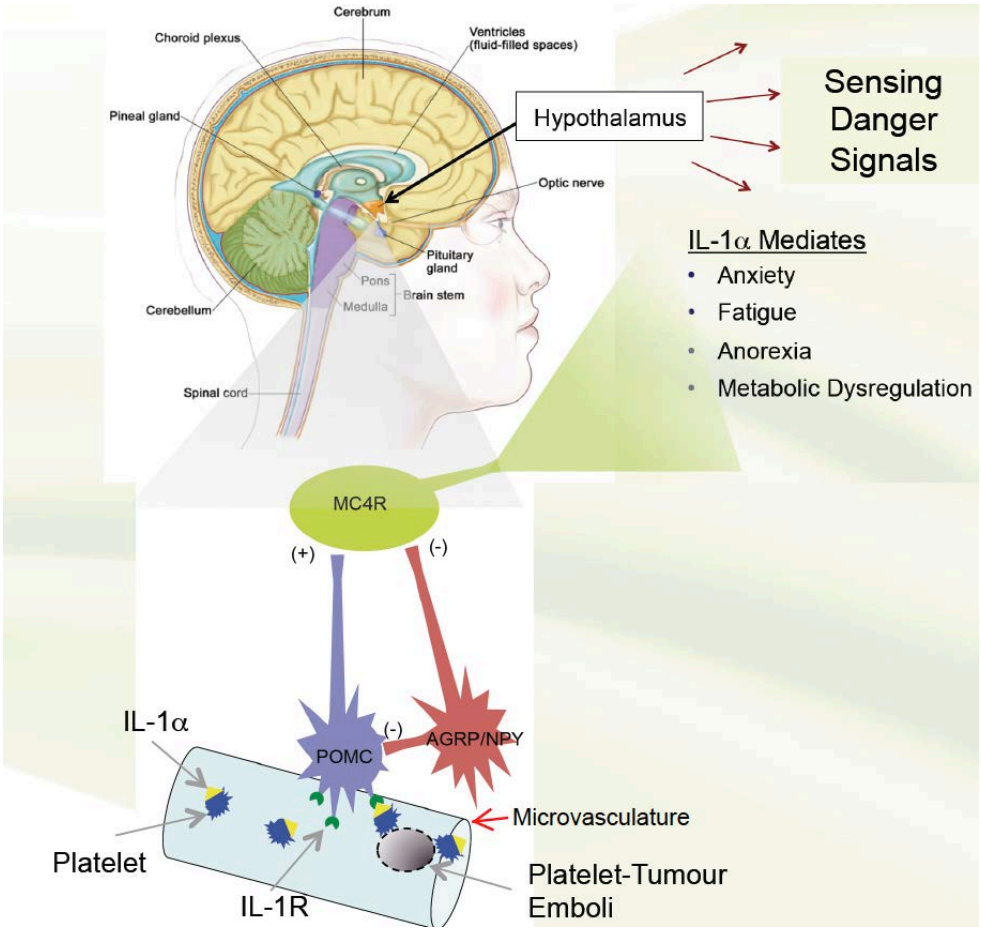
Tumor cells travel with lymphatic drainage or penetrate the basement membrane to reach the circulation. In the circulation "sticky" tumor cells can interact with and adhere to platelets to form tumor-platelet micro-emboli. Inhibition of IL-1α signaling in the tumor microenvironment is thus expected to inhibit tumor growth by blocking IL-1α effects on tumor survival, neoangeogenesis and tissue matrix remodeling.

Figure 1.3: IL-1α Role in Hematogenous Spread and Metastasis



Tumor-platelet aggregates or "microemboli" are formed by the adherence of tumor cells and platelets via membrane glycoprotein interactions[23]. By adhering platelets on their surface, tumor cells hijack the platelets ability to activate vascular endothelium. IL-1α present on the surface of platelets plays a role in activating vascular endothelium and facilitating transendothelial migration of tumors. Thus the platelet-IL-1α system provides a mechanism for invasion of circulating tumors into tissue to form new sites of metastasis[24,25]. Inhibition of IL-1α mediated platelet activation of the vascular endothelium is expected to reduce the potential for tumors to extravasate the blood vessel and penetrate into tissue. Therefore, reducing the metastatic potential of tumors.

Figure 1.4: Role for IL-1α in Metabolic Dysregulation



Platelet-tumor microemboli interact with endothelial cells of microvasculature in the arcuate nucleus. IL-1α on the surface of microemboli can trigger IL-1 receptors on VE. However, fenestrations in the microvasculature of the hypothalamus are also penetrated by neuronal cells that express IL-1 receptor[26]. These cells, such as the POMC neurons, can respond to IL-1 stimulation to mediate central nervous system control of appetite, metabolism and well-being[27,28,29]. In times of acute stress (such as trauma or illness), these neurons are able to sense "danger" and drive physiological mechanisms that provide enhanced ability to respond to stress, including breakdown of muscle protein for the mobilization of amino acid substrates to provide for gluconeogenesis. When the "danger" signal is chronic, as it is in cancer, this process drives pathologic wasting, including loss of crucial cardiac and diaphragmatic muscle. Treatment with Xilonix™ is expected to reduce IL-1α mediated signaling at the level of the hypothalamus. This will enable the body to normalize metabolic activity and correct the underlying wasting phenotype associated with malignancy.

1.3 REVIEW OF THE IL-1 SYSTEM

Interleukin-1 alpha (IL-1α) is a 20kD protein expressed on the surface of a variety of cells either constitutively or after stimulation. Perhaps most importantly, IL-1α is constitutively found on peripheral blood cells, particularly platelets and monocytes, where it appears to play a crucial role in triggering and sustaining chronic inflammatory responses.

For a more detailed discussion, please see "Review of the IL-1 System" in the Investigator's Brochure.

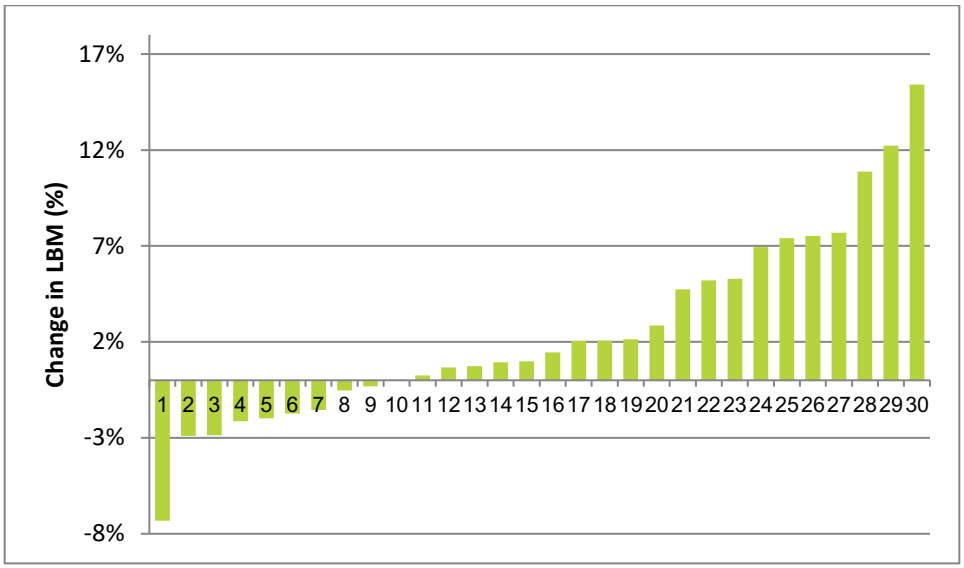
1.4 OBSERVATION IN PREVIOUS STUDY: MABP1 INCREASED LEAN BODY MASS IN PATIENTS WITH REFRACTORY METASTATIC CANCER

Anti-IL-1α therapy was used to treat patients at MD Anderson Cancer Center's so-called Phase I treatment facility in Houston, Texas, which offers the latest in emerging experimental treatments. These were patients with refractory, metastatic disease that had failed a median of 5 regimens of previous therapy. Patients were defined as refractory since they had failed all standard of care therapy and had no remaining therapeutic options that would be expected to provide benefit.

Of the 24 patients that were restaged according to RECIST criteria, an overall response rate of 37% (9/24) was achieved (defined as stable disease or better for ≥ 3 months). 10 NSCLC patients were restaged using the immune related response criteria (irRC), and a 20% (2/10) response rate was observed. Out of these 34, 30 patients complied as scheduled with DEXA scans both at screening and at the 8-week follow-up assessment.

Analysis of baseline and follow-up DEXA scans showed the remarkable finding that most patients, 70% (21/30), had objective increases in lean body mass (LBM). Responders showed an average LBM improvement of 1.9±2.0 kg ($p<0.001$) compared to their baseline values, while the average change for the entire cohort was 1.0 kg ($p=0.02$)

Figure 1.5

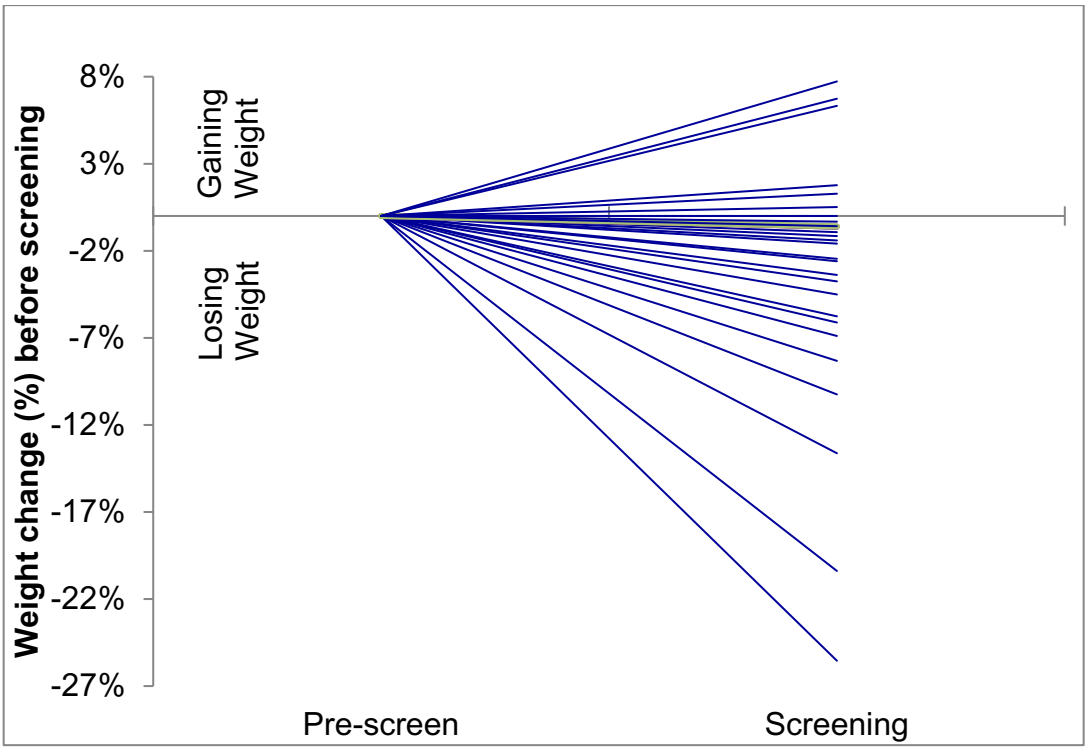


Most patients (21/30 or 70%) showed increase in lean body mass (LBM) of 1.9±2.0 kg after three infusions of antibody therapy ($p<0.001$). Patients were evaluated with DEXA no more than 2 weeks prior to the start of treatment. Each bar represents the change in LBM for a single patient. Lean body mass change is expressed as a percentage of total body weight from baseline.

In the current study, most patients that entered study had dramatic loss in body weight prior to enrollment, which is presumed to have been primarily muscle mass (See Figure 1.6). A reversal of this muscle wasting is not known to occur in patients with refractory metastatic disease. To our knowledge, there are no reports in the literature of an agent able to facilitate increases in LBM at this stage of disease.

Regulation of energy balance is known to be orchestrated by the central nervous system (CNS), via the hypothalamic-pituitary-adrenal axis (HPA). Since IL-1 signaling is known to trigger cachexia via signaling at the hypothalamus, these results point to a correction of the IL-1-driven inflammatory signaling at the hypothalamus.

Figure 1.6



Each line represents the trajectory of body weight for each patient. Patient body weights at least 6 months prior to screening for the current study are represented as 100%, and compared to that measured during the study screening/enrollment process. The steep negative slope shows that the large majority (23/30, 77%) of patients were experiencing significant body weight loss upon entry into the study. Prior body weights were obtained from medical records.

The results reported here are particularly remarkable. First, these results provide the most substantive evidence to date that an anti-inflammatory therapy can target the malignant inflammation that drives muscle catabolism in patients with cancer-associated cachexia. This result was also obtained in an advanced, heavily pre-treated (median=5 previous chemotherapeutic regimens) cancer population who had lost a mean of 5% of their body weight in the previous 6 months before entering the trial. Finally, the drug was well tolerated with few possibly drug related AEs, no infusion reactions, and only one possibly drug related SAE (lung

infection in patient with disseminated NSCLC). Treatment with Xilonix™ is thus expected to provide a safe and effective treatment option to treat refractory cancer patients.

1.5 ANALYSIS OF COLORECTAL COHORT

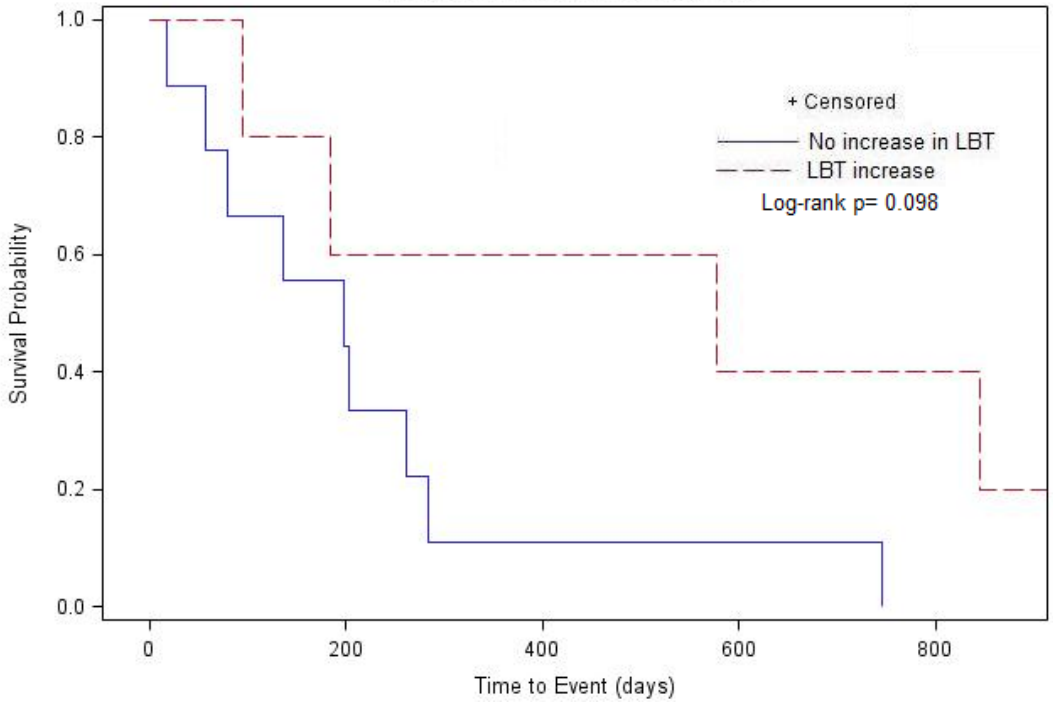
A large proportion of patients enrolled and treated in this pilot trial had refractory metastatic colorectal cancer (14 out of 52). Five of these CRC patients responded with an increase in LBM, and the average increase was 4.6%.

Among the 14 subjects with colorectal carcinoma, the median overall survival was 6.7 months for the intent to treat population (which included three patients enrolled with waivers) and 8.7 months for the per-protocol population.

Median survival duration correlated strongly with increases in LBM. For those with an objective evidence of an increase in LBM from baseline to week 8, the median survival duration was 19.3 months. This is in sharp contrast to a median OS of 6.6 months seen in those with no evidence of LBM increase. While the single arm design of the trial does not enable us to conclude that the increased survival was the result of drug effect, it does strongly suggest that an increase in LBM in this advanced population will correlate favorably with survival.

Subjects enrolled in this trial were also evaluated for tumor response using RECIST 1.1. As a result, subjects were discontinued due to radiographic evidence of disease progression. This resulted in the discontinuation of some patients who were potentially experiencing clinical benefit in the form of increased LBM. Had these subjects been allowed to continue on study and further receive drug it might be expected that these responses would have translated into even more significant clinical and survival benefit.

Figure 1.7

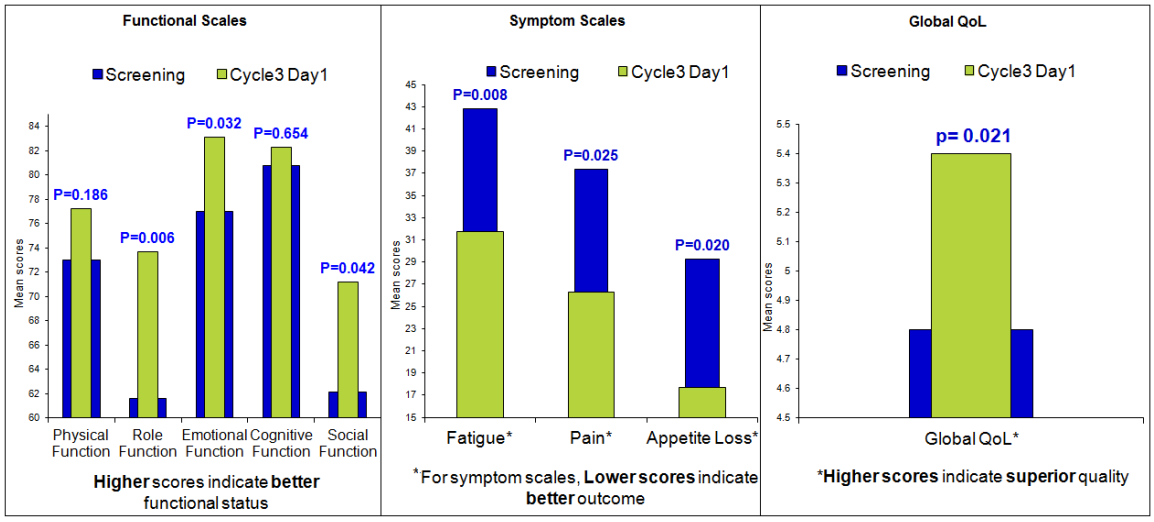


Kaplan–Meier curve showing survival among colorectal cancer patients (n=14) according to evidence of LBM increase. 5 of 14 (36%) responded with an increase in LBM after just 8 weeks (3 infusions). Those with LBM increase had a median OS of 19.3 months vs 6.6 months in those who lost LBM.

1.6 QUALITY OF LIFE ANALYSIS

Quality of life (QoL) was assessed using the EORTC QLQ-C30 questionnaire. QoL assessments were performed at baseline and prior to follow up DEXA scans. This information was available for 33 patients. Several domains of this instrument showed improvement in this patient population--including social, emotional, and role functions. At the same time, a robust decrease in the symptoms of fatigue, pain, and appetite loss were observed. The absolute score point reductions were 11.1 (p=0.008), 11.1 (p=0.025), and 12.5 (p=0.02), respectively. And finally, an improvement in Global QoL was achieved, and this result was statistically significant (p=0.02). These findings are summarized in figure 1.8.

Figure 1.8



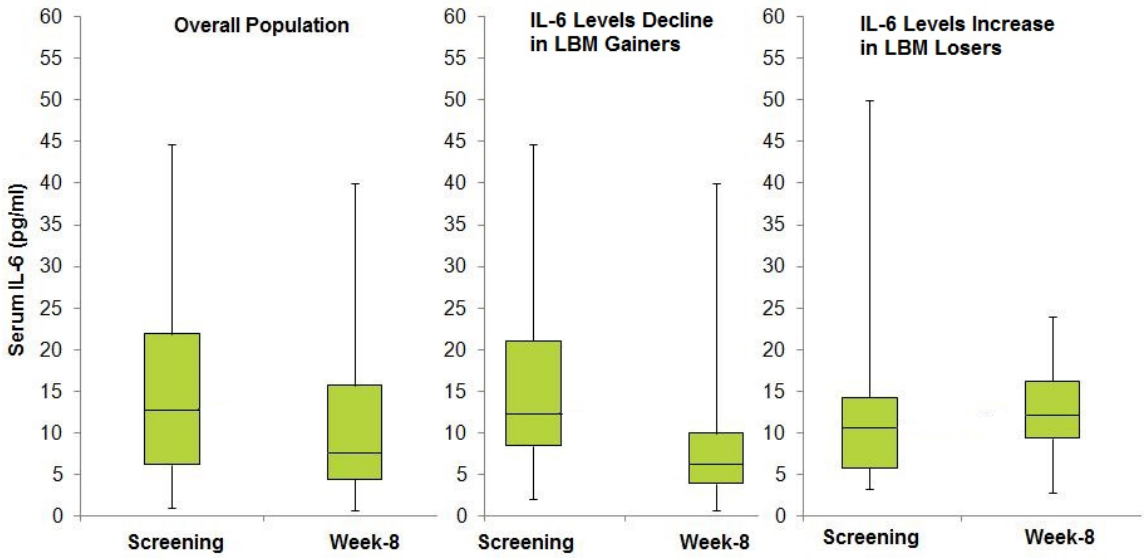
Change in quality of life as assessed by EORTC QLQ-30 questionnaire. Emotional, Social, and Role functions improved significantly at week 8 showing an average increase of 6.1±15 (p=0.032), 9.1±24 (p=0.042), and 12.1±23 (p=0.006) respectively. Substantial reduction on fatigue (-11±22, p=0.008), pain (-11±27, p=0.025), and appetite loss (-12.5±29, p=0.02) was observed during this period. The Global QoL increased from 4.8 to 5.4 (0.6 score points, p=0.02).

1.7 CORRELATIVE ANALYSIS

Analysis of serum cytokine levels has shown a reduction in IL-6 levels after treatment with Xilonix™. Of the 52 subjects, 43 had data available from screening and at week 8. One subject with Castleman's disease, however, was not included in the analysis as their serum levels were 150 times greater than the cohort average. The mean serum IL-6 levels for these 42 subjects was 20.8±23.4 (median 12.8) pg/ml, which decreased to a mean of 15.9±27.1 (median 7.6; p=0.08) after 8 weeks of treatment. This decrease was even more pronounced when stratified by LBM response. IL-6 levels for subjects who increased LBM (N=20) changed from an average of 16.5±12.5 (median of 12.3) to an average of 10.9±12.9 (median of 6.2 pg/ml; p=0.044). Those

subjects who did not respond had non-statistically significant increases in IL-6 levels. Figure 1.9 details these responses.

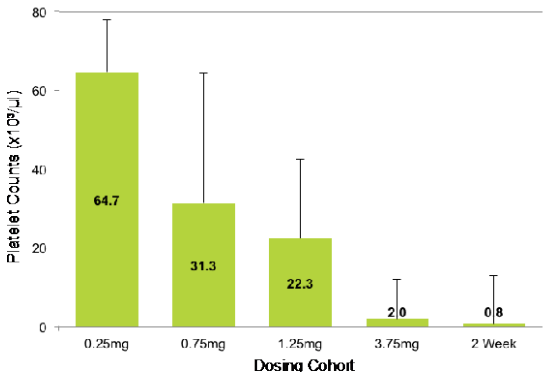
Figure 1.9



Plasma IL-6 levels were measured by ELISA. Overall for the entire patient population, plasma IL-6 levels declined. However, stratification of the data among patients that had increases in LBM versus those that lost LBM revealed differences. LBM increase was associated with declining serum IL-6 at week 8, while patients with LBM loss did not show reduction in plasma IL-6 levels (Overall population (n=43): Average change -4.9±26 (median -2.7) pg/ml, p=0.08; Responders (n=20): Average change -5.6±13 (median -3.2) pg/ml, p=0.044; Non- responders (n=6): Average change -3.8±21 (median -0.4) pg/ml, p= 0.91).

IL-1α is expressed on the surface of platelets, thus platelet numbers were analyzed across dose cohorts. Increases in platelet counts are known to occur in many advanced cancer patients, and can be a prognosticator of disease progression[30]. In this trial, platelet counts appeared to increase over time (Figure 1.10), however, there also appeared to be dose dependent abrogation of platelet compartment expansion. This is the likely result of decreasing serum IL-6 levels, as there was no evidence of platelet destruction in these patients.

Figure 1.10



Platelet counts were determined as part of routine blood analysis. Platelet numbers showed a trend of increasing over time in advanced cancer patients and can be a prognosticator disease progression. Platelet counts presented are differences between those measured prior to treatment and at week 8 (after three rounds) of antibody therapy. The 3.75mg/kg dose cohort was initially provided every three weeks. This dosing was increased in frequency to every two weeks (2 week).

Flow cytometry was also used to examine IL-1α expression on CD14+CD16+ monocytes. Treatment with Xilonix™ resulted in a trend of reducing IL-1α+CD14+CD16+ monocytes (as a percentage of CD14+CD16+). This reduction was observed without an overall decrease in the absolute number of monocytes, which suggests Xilonix™ binding to IL-1α on the surface of these potentially pathogenic cells. Decreases in IL-1α+CD14+CD16+ monocytes appeared to rebound towards the end of dosing cycles (Figure 1.11).

Figure 1.11

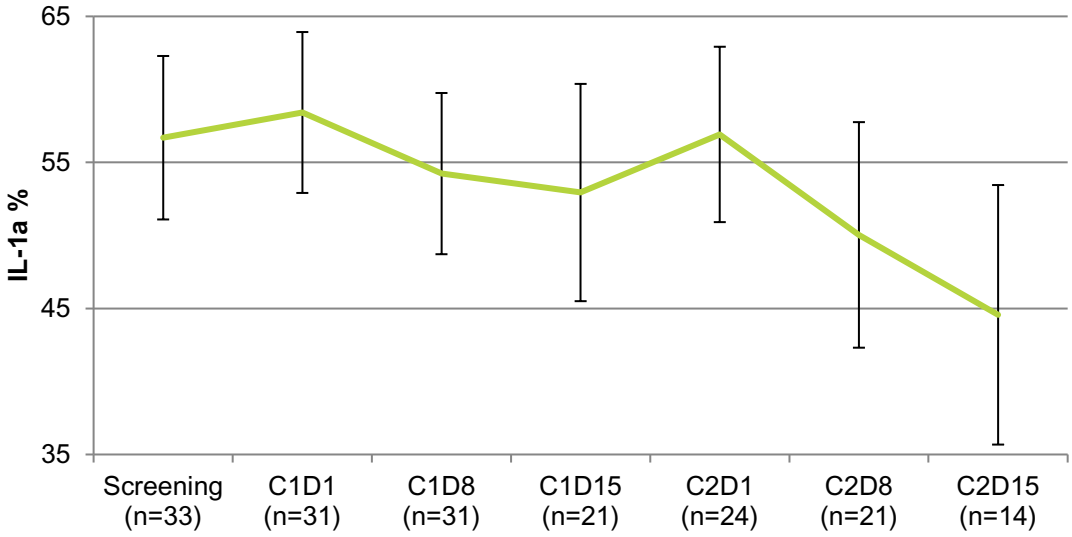


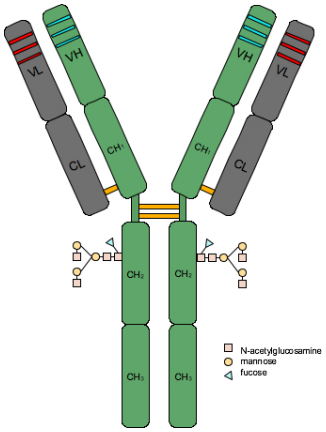
Chart shows IL-1α expressing monocytes present in peripheral blood as percentage of CD14+CD16+ monocytes. Blood samples were analyzed from patients at screening, prior to infusion with Xilonix™, until cycle 5, day one post infusion (C2D15). The n values change over time, as patients are lost from study. Trend appears to show treatment reduction in exposed IL-1α present on this monocyte subset.

2. INVESTIGATIONAL PRODUCT

2.1 ACTIVE INGREDIENT, PHARMACOLOGIC CLASS, STRUCTURE

The active ingredient in the drug product Xilonix™ is MABp1, a recombinant human IgG1 monoclonal antibody specific for human interleukin-1α (IL-1α). The entire MABp1 heavy and light chain sequences are identical to those found in naturally-occurring human IgG1κ, with the light and heavy chain variable regions being identical to those originally expressed by a peripheral blood B lymphocyte that was obtained from a healthy individual.

Figure 2.1: MABp1 Antibody



The MABp1 primary glycoform has a molecular weight of 148.1 kilodaltons. Like all IgG1 molecules, the heavy chains are joined at their hinge regions through two disulfide linkages, and each heavy chain is joined to one light chain through one disulfide linkage between their CH_1 and CL domains respectively.

The main isoform has a pI of about 9.2 and comprises about 70-80% of the total isoform population in all lots that have been manufactured to date, as determined by capillary isoelectric focusing. The heavy chain CH_2 domains are glycosylated primarily with the oligosaccharide structure shown in Figure 2.1, as determined by mass spectroscopy of the cleaved glycans. The glycosylated residue (Asn-302 as numbered from the N-terminus of MABp1) has been determined by peptide mapping to be in the same highly conserved N-linked glycosylation site as found in endogenous IgG1 (Asn-297 according to the generic numbering system). Similarly, the primary glycan, commonly referred to as G0F, is the same as that found on about 22% of endogenous human IgG molecules[31].

The entire MABp1 heavy and light chain sequences are identical to those found in naturally-occurring human IgG1κ, with the light and heavy chain variable regions being identical to those originally expressed by a peripheral blood B lymphocyte that was obtained from a healthy individual.

Endogenous anti-IL-1α antibody has been reported in 5% to 28% of healthy serum or plasma samples[32,33]. It has been measured in cord blood, children and adults[34]. The anti-IL-1α antibodies

measured in human plasma have been strictly of the IgG class, particularly IgG1, IgG2, and IgG4. Relatively equal distribution is seen in male and female plasma[35]. Binding affinities reported for endogenous anti-IL-1α antibodies, ranging from 4 to 16 pM, are comparable to that for MABp1, the specification for which is 22 to 260 pM.

It is important to point out that affinity maturation had already taken place in the human host, and therefore no *in vitro* affinity maturation was required to increase the natural binding affinity of MABp1. Also important is the fact that, unlike most other therapeutic IgG products, for which the Fc regions are derived from a rare human allele, XBiotech's product includes a heavy chain in which the constant (CH) region represents an allele found in approximately 70% of the human population. These two features should make for a drug product with reduced potential for immunogenicity.

2.2 DRUG PRODUCT (XILONIX™) DESCRIPTION

XBiotech's proposed drug product, Xilonix™, is a sterile injectable liquid formulation of 50 mg/mL MABp1 in a stabilizing isotonic buffer (pH 6.4). Each 10-mL serum vial contains 6 mL of the formulation, and is sealed with a 20-mm grey bromobutyl stopper and flip-off aluminum seal. Product should be stored at 2-8°C in the dark, with excursions to room temperature permitted in order to prepare the drug product for use. The exact composition of the drug product is shown below:

Composition of the Final Drug Product			
Ingredient	**Grade**	**Manufacturer**	**Concentration**
MABp1 antibody	GMP	XBiotech	50 mg/mL
sodium phosphate dibasic	compendial	JT Baker	12 mg/mL
citric acid monohydrate	compendial	JT Baker	2 mg/mL
Trehalose•$2H_2O$ (high-purity low endotoxin)	compendial	Ferro- Pfanstiehl	60 mg/mL
polysorbate 80	compendial	JT Baker	0.2 mg/mL
Phosphoric acid, to adjust pH	compendial	JT Baker	0.04 mg/mL
water for injection	compendial	Irvine Scientific (USA)	- -

2.3 DESCRIPTION AND COMPOSITION OF PLACEBO PRODUCT

The placebo product is manufactured following the same procedures and batch records used to manufacture the MABp1 drug product. The placebo dosage form is a sterile isotonic formulation buffer at pH 6.2-6.5. Each 10-mL Type I borosilicate glass serum vial contains 6mL of the formulation buffer, and is sealed with a 20-mm Daikyo Flurotec butyl rubber stopper and flip-off aluminum seal. The product should be stored upright at 2-8°C in the dark, with excursions to room temperature permitted in order to prepare the drug product for use. The exact composition of the Placebo Product is shown in the table below:

Composition of Placebo Product			
Ingredient	**Grade**	**Manufacturer**	**Concentration**
trehalose dihydrate	compendial	Ferro-Pfanstiehl (USA)	60 mg/mL
sodium phosphate dibasic	compendial	JT Baker (USA)	12 mg/mL
citric acid monohydrate	compendial	JT Baker (USA)	2 mg/mL
Polysorbate 80	compendial	JT Baker (USA)	0.2 mg/mL
Phosphoric acid, to adjust pH	compendial	JT Baker	0.04 mg/mL
water for injection	compendial	Irvine Scientific (USA)	q.s.

2.4 STORAGE

The recommended storage condition is upright in the dark, at 2-8°C.

2.5 STABILITY

The drug product is formulated in a buffer in which most of the tonicity comes from trehalose rather than salt. Trehalose is an effective stabilizer against oxidation, aggregation, thermal, and mechanical stress. Citrate was selected as the buffering agent due to its antioxidant properties. Extensive stability data indicates that the drug product is very stable, even under thermally and mechanically stressed conditions. Short excursions to room temperature have shown no negative effect on the product. However, the study treatment products are not to be frozen at any time. The drug product has been shown to be stable for up to 24 hours at room temperature after dilution in 100 ml of normal saline, although it is recommended to store at 2-8°C after dilution whenever feasible. The study treatment products are currently labeled with a 12-month retest date.

2.6 METHOD OF ADMINISTRATION

IV Administration

Xilonix™ should be diluted in a 100-mL bag of normal saline prior to infusion. The following calculations must be used to determine the volume of drug product to be diluted for each study subject:

50 mg/ml drug product, 7.5 mg/kg dose:

Volume of drug product to be diluted = **Vd** = $\frac{\text{Body Weight X Dosage}}{\text{50 mg/mL}}$

(Body Weight should be rounded to the **nearest whole number**)

Example for 70 kg Subject at 7.5 mg/kg: **Vd** = $\frac{\text{70 kg X 7.5 mg/kg}}{\text{50 mg/mL}}$

Vd = 10.5 mL (round to **one decimal place**)

The calculated volume (**Vd**) should be withdrawn from the subject's assigned vial(s) using a suitable syringe. The same amount of saline as the calculated drug should be removed from the 100-ml bag. The calculated volume is then injected into the 100-mL IV bag of normal saline

(0.9% NaCl), resulting in a final total volume of 100 ml. The drug product should then be mixed by gently inverting the bag ten times.

After priming the infusion set lines, the delivery pump should be programmed to deliver 100 mL of the diluted drug product over a 1-hour period (60 ± 15 minutes), with the subject being monitored for signs of an infusion reaction. **The infusion should be chased with a minimum of 30 mL of normal saline to deliver any product that may be held up in the dead volume of the infusion set.**

***IMPORTANT*:**

(1) The actual body weight of the subject on Cycle 1 Day 1, rounded to the nearest whole number, must be used in calculating their individual dosage. The same dosage calculated at C1D1 will be administered at each cycle visit following C1D1.

(2) Some subjects may require more than one vial for a single infusion, depending on their body weight.

(3) The diluted product must be administered the same day that it is diluted.

2.7 AGENT ORDERING

The Responsible Investigational Pharmacy will order study drug (Xilonix™ or placebo) from XBiotech as needed.

2.8 POTENTIAL DRUG INTERACTIONS

There are no known drug interactions with MABp1. In controlled trials that combined the use of IL-1ra with TNF inhibitors, a higher incidence of serious infection was noted. MABp1 has not been administered concomitantly with these agents in clinical trials. However, due to potential risk, it is not recommended that MABp1 be used in combination with anti-TNF agents.

There are significant number of platelets and peripheral blood mononuclear cells that may be targeted by MABp1. Thus, there is the potential for MABp1 to cause thrombocytopenia, monocytopenia or neutropenia. However, to date, there has been no evidence that MABp1 can cause cytopenia of any kind.

2.9 PROHIBITED AND RESTRICTED THERAPIES

The following concomitant therapies are prohibited while on trial:

- Therapeutic agents and biologics that target the IL-1 or TNF-alpha system
- Live virus vaccines
- Investigational agents
  Any radiation and/or chemotherapyNote: Concomitant palliative radiotherapy is allowed only if index lesions, and measurable new lesions, as defined by the immune related response criteria, are not included within the radiation field

3. STUDY DESIGN AND OBJECTIVES

This is a phase III, double blind, placebo controlled, randomized, pivotal trial of the True Human monoclonal antibody MABp1 in subjects with refractory, metastatic colorectal cancer.

Enrolled subjects will be randomized to receive either MABp1 plus best supportive care (BSC) or placebo plus BSC. BSC is defined as those measures intended to provide palliation of symptoms and improve quality of life. This includes, but is not limited to, antibiotics, anti-emetics, narcotics, and parenteral nutrition.

The study will compare the overall survival (OS) between the MABp1 treated and placebo arms. Secondary endpoints will include change in lean body mass from screening to the cycle 5 assessment and change in quality of life. Other secondary endpoints will be progression-free survival, response rate, disease control rate, and stabilization of platelet counts. LBM will be assessed through the use of dual-energy X-ray absorptiometry (DEXA) scans. Quality of life will be assessed with the EORTC QLQ-C30 (v.3). Response and progression will be evaluated using the Immune Related Response Criteria (irRC).

Study Objectives:

Primary Efficacy Endpoint

- Overall survival (OS) will be the primary endpoint of this study, which will be measured from the date of randomization until death or last follow-up.

Secondary Efficacy Endpoints

- Secondary efficacy variables will include change in lean body mass (LBM) measured by dual-energy X-ray absorptiometry (DEXA) scans, change in Quality of Life assessed through the cancer-specific EORTC QLQ-C30 questionnaire, stabilization of platelet counts, progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR).

4. ELIGIBILITY CRITERIA

No waivers/exemptions will be granted for protocol inclusion/exclusion criteria.

4.1 INCLUSION CRITERIA

Subjects may be included in the study if they meet all of the following criteria:

1. Subjects with pathologically confirmed colorectal carcinoma that is metastatic or unresectable and which is refractory to standard therapy. To be considered refractory, a subject must have experienced progression (or intolerance) after treatment with all of the following agents: oxaliplatin, irinotecan flouropyrimidine, and cetuximab or panitumumab if KRAS wildtype.
2. Subjects will not be treated with any radiation, chemotherapy, or investigational agents while enrolled in this protocol.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.
4. At least 2 weeks since the last previous cancer treatment including: chemotherapy, radiation therapy, immunotherapy, surgery, hormonal therapy, or targeted biologics and 4 weeks for patients who received treatment immediately prior to the study with anti-IL-1 or anti-TNF agents.
5. Age ≥ 18 years, male or female subjects.
6. Serum potassium and magnesium levels within institutional normal limits. Total serum calcium or ionized calcium level must be greater than or equal to the lower limit of normal. Subjects with low potassium, calcium and magnesium levels may be replenished to allow for protocol entry.
7. Adequate renal function, defined by serum creatinine ≤ 1.5 x ULN.
8. Adequate hepatic function defined as:
    - total bilirubin ≤ 1.5 times the institutional upper limit ULN.
    - alanine aminotransferase (ALT) ≤ 2.0 times the institutional ULN.
    -
    - **Exception**: subjects with known liver metastases: ≤ 3.0 times the institutional ULN for ALT.
9. Adequate bone marrow function as defined as:
    - absolute neutrophil count (neutrophil and bands) of ≥ 1,500/mm^3 (≥ 1.5 x 10^9/L)
    - platelet count of ≥ 100,000/mm^3 (≥ 100 x10^9/L)
    - hemoglobin of ≥ 9 g/dL
10. For women of childbearing potential (WOCBP), a negative serum pregnancy test result at Screening and monthly thereafter.

For women who are not postmenopausal (24 months of amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to use adequate methods of contraception, during the treatment period and for at least 1 month after the last dose of study drug.

Acceptable contraceptive measures include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: Oral, Intravaginal or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation; Oral, injectable, implantable, intrauterine device (IUD), intrauterine hormone-releasing system(IUS)

- Barrier or sterilization methods such as condoms, bilateral tubal occlusion, vasectomized partner or sexual abstinence

For men: agreement to use a barrier method of contraception during the treatment period and for at least 1 month after the last dose of study drug

11. Signed and dated institutional review board (IRB)-approved informed consent before any protocol-specific screening procedures are performed.
12. Patients enrolled must, in the Investigator's judgment, be healthy enough to stay on the clinical trial for three months.

4.2 EXCLUSION CRITERIA

Subjects will be excluded from the study if they meet any of the following criteria:

1. Mechanical obstruction that would prevent a patient from receiving adequate nutritional intake.
2. A serious uncontrolled medical disorder or active infection that would impair the ability of the patient to receive protocol therapy.
3. Uncontrolled or significant cardiovascular disease, including:
    - A myocardial infarction within 6 months
    - Uncontrolled angina within 3 months
    - Congestive heart failure within 3 months defined as NYHC-II
    - Diagnosed or suspected congenital long QT syndrome
    - Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, Wolff-Parkinson-White (WPW) syndrome, or torsade de pointes). Prolonged QTc interval on pre-entry electrocardiogram (>450 msec). If the automated reading is prolonged (i.e., >450 msec), the EKG should be manually over-read.
    - Any history of second or third degree heart block (may be eligible if currently have a pacemaker)
    - Heart rate <50 beats per minute on pre-entry electrocardiogram
    - Uncontrolled hypertension (blood pressure >140 mm Hg systolic and >90 mm Hg diastolic).
4. Dementia or altered mental status that would prohibit the understanding or rendering of informed consent.
5. Subjects who have not recovered from the adverse effects of prior therapy at the time of enrollment to ≤ grade 1; excluding alopecia and grade 2 neuropathy.
6. Immunocompromised subjects, including subjects known to be infected with human immunodeficiency virus (HIV).
7. Known hepatitis B surface antigen and/or positive hepatitis C antibody and presence of hepatitis C RNA.
8. History of tuberculosis (latent or active) or known positive Interferon-gamma release assay (IGRA).
9. Receipt of a live (attenuated) vaccine within 1 month prior to screening.
10. Subjects with history of hypersensitivity to compounds of similar chemical or biologic composition to Xilonix™.
11. Women who are pregnant or breastfeeding.

12. WOCBP or men whose sexual partners are WOCBP who are unwilling or unable to use an acceptable method of contraception for at least 1 month prior to study entry, for the duration of the study, and for at least 1 month after the last dose of study medication.
13. Weight loss >20% in the previous 6 months.
14. History of progressive multifocal leukoencephalopathy or other demyelinating disease
15. Subjects on immunosuppressive therapy, including transplant patients

5. TREATMENT PLAN

This is a phase III, multicenter, double blind, randomized, placebo controlled pivotal trial of the True Human monoclonal antibody MABp1 in subjects with metastatic colorectal cancer who are refractory to standard therapy.

- Enrolled subjects will be randomized (2:1) to receive either MABp1 plus best supportive care (BSC) versus placebo plus BSC.
- BSC is defined as those measures intended to provide palliation of symptoms and improve quality of life. This includes, but is not limited to, antibiotics, anti-emetics, narcotics, and parenteral nutrition.
- Subjects randomized to MABp1 or placebo will receive 7.5 mg/kg of study drug via intravenous infusion once every 2 weeks (one cycle).
- Study drug will be administered under close observation in a facility equipped to handle medical emergencies. Subjects must be observed for at least 1 hour with stable vital signs following the end of the infusion.
- Efficacy will be assessed by measuring the difference in median overall survival (OS) between the MABp1 and placebo groups.
- Secondary endpoints will include change in lean body mass (LBM) from baseline to cycle 5, change in Quality of Life, stabilization of platelet counts, progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR). Lean body mass measurements will be obtained through the use of dual-energy X-ray absorptiometry (DEXA) scans. Quality of life will be assessed with the EORTC QLQ-C30 (v. 3). Response and progression will be evaluated using the Immune Related Response Criteria (irRC).
- Safety assessments will include physical examinations, vital signs, standard clinical laboratory evaluations (blood chemistry, urinalysis, and hematology), allergic reaction monitoring and adverse event monitoring.
- Pharmacokinetics samples will be taken in all patients. The pharmacokinetics of MABp1 in plasma will be randomly analyzed. Plasma samples will also be randomly monitored for the development of anti-MABp1 antibodies. If the study meets the primary endpoint, then all samples will be tested.

5.1 DOSE MODIFICATIONS

Subjects will be monitored continuously for adverse events (AEs) while on study therapy. Subjects will be instructed to notify their physician immediately for any and all AEs. Adverse events will be graded according to CTCAE version 4.0. Dose modifications will be made for:

a) Subjects who experience an adverse event of grade 3 or greater that is probably related to the study drug will be withdrawn from study and will be followed until the resolution of toxicity.

b) Subjects who experience an adverse event of grade 3 or greater that is possibly related to the study drug will not be retreated with subsequent cycles until the adverse event resolves to grade 1 or less. Subjects who require greater than 14 days of treatment delay due to toxicity that is possibly related to the study drug will be removed from the study and followed until resolution of toxicity.

5.2 DISCONTINUATION OF THERAPY

Study therapy MUST immediately be discontinued for any the following reasons:

- Radiographic evidence of tumor progression as defined by the Immune Related Response Criteria (see section 7.5)
- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality, inter-current illness, or progression of disease which, in the opinion of the Principal Investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by the sponsor
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Subjects will also be discontinued based on 5.1a.

5.3 EMERGENCY UNBLINDING

Subjects and Investigators will be unblinded as to treatment allocation after **all patients** have completed the study and the **database is locked** (routine unblinding). In the event of an emergency that would require the investigator to be aware of the treatment allocation prior to the end of the trial, the investigator can obtain this information, on a per Patient basis, from the Sponsor's electronic database at the Investigative site. The investigator is not required to contact the sponsor or sponsors representative prior to unblinding, but is encouraged to do so if there are any questions regarding the unblinding procedure or need to unblind.

Examples of events that would qualify as emergent are as follows:

- A grade 3 or greater AE which are "probably or definitely" related to study drug administration, such as a grade 3 infusion reaction, **and** where treatment assignment information is essential for the management of the event. Per section 5.1 (a), this type of reaction would require that the patient receives no further doses, and is followed until the resolution of the toxicity.
- Any suspected, unexpected, serious adverse reaction (SUSAR)
- Pregnancy

5.4 STUDY PROCEDURES

Screening-14 days are allowed to complete all procedures and the first dose (C1D1) must occur within 7 days of randomization:

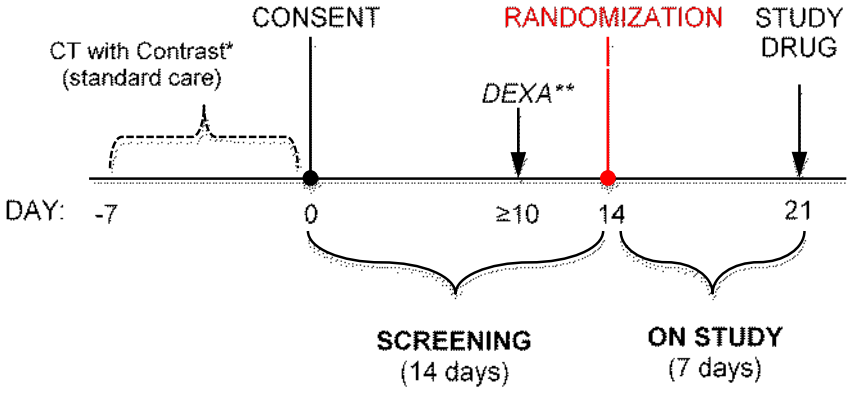
- Informed Consent
- Medical History
- Physical Exam
- Height
- Weight
- Vital Signs
- ECOG Evaluation
- Hematology panel: CBC with differential and platelets
- Chemistry panel
- PT/aPTT/INR
- Urinalysis
- Serum Pregnancy
- C-Reactive Protein
- EORTC QLQ-C30
- Prior Medications
- TNM staging
- Randomization- after confirmation that subject meets all inclusion/exclusion criteria
- DEXA Scan- Lean Body Mass/Body Composition
- Tumor Measurements- Assessments can include CT or MRI, and whichever modality is chosen for the initial tumor assessment must be used for the week 8 assessment. The choice of modality should be based primarily on the type of scan that the patient has previously received as their standard of care. Standard of care scans obtained within 28 days prior to C1D1 may be used as screening scans.

DEXA scans should be scheduled to occur prior to CT or MRI tumor measurements. In the event that these scans are obtained prior to the DEXA scan (such as scans done for standard of care), then there must be a 10 day washout prior to obtaining the DEXA scan.

PT023: Screening and Randomization

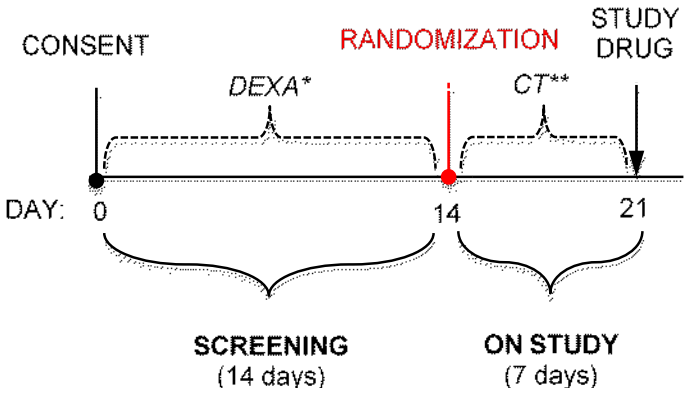
Options pertaining to CT Availability

A. CT Available Before Screening (within 28 days of dosing)



*CT with Contrast (standard of care) performed within 28 days prior to treatment on study may be used as the Baseline Scan.
**DEXA should be completed no earlier than 10 days after CT with Contrast (standard care).

B. CT Unavailable Before Screening



*DEXA may be completed anytime during Screening before Randomization.
**Protocol-required CT may be completed anytime after Randomization but before the first dose of study drug.

Note: These schema show the maximum window sizes for completion of the radiologic procedures. The key elements are:

- ***Baseline tumor assessment should be done within 28 days of C1 D1***
- ***A 10 day washout period is required for DEXA scans acquired after a CT***
- ***Alternatively, the DEXA scan can be obtained prior to tumor measurements***

Cycle 1 Day 1 (C1D1):

- Physical Exam
- Weight
- Vital Signs (pre-infusion)
- ECOG Evaluation
- Hematology panel: CBC with differential, platelets (pre-infusion)
- Chemistry panel (pre-infusion)

*Urinalysis, Hematology and Chemistry panels that are obtained for the purpose of screening a subject, and that are drawn within 72 hours of C1D1, may also be used for the C1D1 baseline safety lab values.

- Urinalysis (pre-infusion)
- CRP (pre-infusion)
- PK Sampling (pre-infusion)
- Study Drug infusion
- Vital signs (60 minutes post-infusion)
- PK Sampling (30-90 minutes post-infusion)
- Adverse Event monitoring
- Concomitant Medications

Cycle 2 Day 1 +/- 2 days (C2D1):

- Physical Exam
- Weight
- Vital Signs (pre-infusion)
- ECOG Evaluation
- Hematology panel: CBC with differential, platelets (pre-infusion)
- Chemistry panel and serum pregnancy (pre-infusion same tube)
- Urinalysis (pre-infusion)
- CRP (pre-infusion)
- PK Sampling (pre-infusion)
- Study Drug infusion
- Vital signs (60 minutes post-infusion)
- PK Sampling (30-90 minutes post-infusion)
- Adverse Event monitoring
- Concomitant Medications

Cycle 3 Day 1 +/- 2 days (C3D1):

- Physical Exam
- Weight
- Vital Signs (pre-infusion)
- ECOG Evaluation
- Hematology panel: CBC with differential, platelets (pre-infusion)
- Chemistry panel (pre-infusion)
- Urinalysis (pre-infusion)
- CRP (pre-infusion)
- PK Sampling (pre-infusion)

- Study Drug infusion
- Vital signs (60 minutes post-infusion)
- PK Sampling (30-90 minutes post-infusion)
- Adverse Event monitoring
- Concomitant Medications

Cycle 4 Day 1 +/- 2 days (C4D1):

- Physical Exam
- Weight
- Vital Signs (pre-infusion)
- ECOG Evaluation
- Hematology panel: CBC with differential, platelets (pre-infusion)
- Chemistry panel and serum pregnancy (pre-infusion same tube)
- Urinalysis (pre-infusion)
- CRP (pre-infusion)
- PK Sampling (pre-infusion)
- Study Drug infusion
- Vital signs (60 minutes post-infusion)
- PK Sampling (30-90 minutes post-infusion)
- Adverse Event monitoring
- Concomitant Medications

Cycle 5 Day 1 +/- 2 days (C5D1):

- Physical Exam
- Weight
- Vital Signs (pre-infusion)
- ECOG Evaluation
- Hematology panel: CBC with differential, platelets (pre-infusion)
- Chemistry panel (pre-infusion)
- Urinalysis (pre-infusion)
- CRP (pre-infusion)
- PK Sampling (pre-infusion)
- Study Drug infusion
- Vital signs (60 minutes post-infusion)
- PK Sampling (30-90 minutes post-infusion)
- Adverse Event monitoring
- Concomitant Medications
- EORTC QLQ-C30
- DEXA scan for lean body mass/body composition (+/- 3 days of C5D1)
- Tumor Measurements (+/- 3 days of C5D1- **AFTER DEXA SCAN**)

Cycle 6+- Follow up visits will occur every 14 days (+/- 2 days) for all subjects who remain on trial:

- Physical Exam
- Weight

- Vital Signs (pre-infusion)
- ECOG Evaluation
- Hematology panel: CBC with differential, platelets (pre-infusion)
- Chemistry panel and serum pregnancy (pre-infusion same tube). Serum pregnancy to be completed every 2 cycles.
- Urinalysis (pre-infusion)
- CRP (pre-infusion)
- PK Sampling (pre-infusion)
- Study Drug infusion
- Vital signs (60 minutes post-infusion)
- PK Sampling (30-90 minutes post-infusion)
- Adverse Event monitoring
- Concomitant Medications
- Tumor Measurements (every 8 weeks, i.e. within 7 days prior to C9D1, C13D1 etc.). Upon documentation of radiographic progression, confirmatory tumor measurements to be repeated at 4 weeks +/- 3 days only for patients who elect to continue on therapy until confirmation of progression. If this scan confirms progression, treatment is to be discontinued. If the confirmatory measurements indicate stable disease or better, the patient may elect to continue treatment with radiographic tumor assessments every 8 weeks from Day 1 of the current treatment cycle until progression.

End of Study Visit- This visit should be completed within 14 days for any subject who elects to come off trial or who comes off due to AEs, toxicities, or decline in performance status:

- Physical Exam
- Weight
- Vital Signs
- ECOG Evaluation
- Hematology panel: CBC with differential, platelets
- Chemistry panel
- Urinalysis
- CRP
- Adverse Event monitoring
- Serum Pregnancy
- PK Sampling
- EORTC QLQ-C30
- Concomitant Medications / Non-Drug Therapies review
- DEXA Scan--for any subject who completes visits at least through C3D1, but discontinues prior to C5D1
- Tumor Measurements--for subjects with clinical progression, every effort should be made to obtain radiographic restaging. If subjects are discontinued due to evidence of progressive disease, then tumor measurements do not need to be repeated.

Follow up for Overall Survival

Subjects, who come off trial for any reason after C1D1, will be contacted by phone after 30 days of the last dosing visit for adverse events and ECOG performance status, and at every 4-6 weeks

there after to assess ECOG performance status. Patients will be considered lost to follow up after 3 documented consecutive unsuccessful contact attempts. Prior to any interim analysis, and once the trial has been completed, any subjects who have been lost to follow up will be queried against the Social Security Administration's Death Master File to determine date of death.

5.4 STUDY CALENDAR

Study Procedures	Screening	Cycles 1-4	Cycle 5	Cycle 6+	End of Study Visit	Follow-Up for Survival
	Day -14 (C1D1) must occur within 7 days of randomization:	Day 1 (+/- 2 days)	Day 1 (+/- 2 days)	Day 1 (+/- 2 days)	Within 14 days of treatment discontinuation	Every 4-6 Weeks
Study Drug Infusion		X	X	X		
Informed Consent	X					
Medical History	X					
Serum Pregnancy Test[d]	X	X[d]	X[d]	X[d]	X	
Physical Exam	X	X	X	X	X	
Height	X					
Weight	X	X	X	X	X	
Vital Signs[a]	X	X[a]	X[a]	X[a]	X	
ECOG Evaluation	X	X	X	X	X	X
Hematology Panel: CBC with differential, platelets	X	X	X	X	X	
Chemistry Panel[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
PT/aPTT/INR	X					
Urinalysis[c]	X[c]	X[c]	X[c]	X[c]	X[c]	
PK Sampling[e]		X[e]	X[e]	X[e]	X[e]	
CRP[f]	X[f]	X[f]	X[f]	X[f]	X[f]	

DEXA Scan[g]	X[g]		X[g]		Only Patients that discontinue between C3D1 and C5D1	
EORTC-QLQ-C30[h]	X		X			
Tumor Measurements[i, j, k]	X[i]		X[i] After DEXA scan	X[i, j] Every 8 Weeks	X[j, k] Unless discontinued for Progressive Disease	
Adverse Events	X					
Concomitant Medications	X					

Footnotes for Study Calendar:

[a] Blood pressure, pulse and temperature. Pre and 60 minutes post infusion.

[b] Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], and SGPT [ALT] will be analyzed locally as standard of care for safety prior to infusion. A second pre-infusion sample must be obtained and shipped to the central lab.

[c] Bilirubin, glucose, ketones, leukocytes, nitrites, blood, pH, specific gravity, protein and urobilinogen will be analyzed will be analyzed locally as standard of care for safety prior to infusion. A second pre-infusion sample must be obtained and shipped to the central lab.

[d] Pregnancy Test Every 2 Cycles. Sample sent to the central lab for chemistry will be used for analysis, no additional blood draw required. Results will be sent from central lab to the site

[e] Pre and post-infusion PK samples to be collected. One 6 ml Na-Heparin tube will be used to collect blood from subjects at each PK sampling time point. Note: during visits when subjects are receiving MABp1, the “post-infusion” sample will be collected between 30-90 minutes post-infusion.

[f] CRP will be assayed from the Chemistry sample on Screening, Cycles 1-5, Cycles 6+, End of Study/Early Termination and Unscheduled Visits.

[g] DEXA scans will be performed at screening and at Cycle 5 Day 1 (+/- 3 days) to assess changes in body composition. To qualify for inclusion, a site’s DEXA should include the following compartments: **bone, fat, and lean**. Results are reported in grams, and should be reported for each extremity, trunk, head, and total, to allow for determination of an axial skeletal muscle index. Patients should be scanned with the **same DEXA machine using the same software version, at each measurement.** DEXA scans should be scheduled to occur prior to CT or MRI tumor measurements. In the event that a CT scan with contrast is obtained prior to a DEXA scan (such as scans done for standard of care), then there must be a **10 day washout prior to obtaining the DEXA scan**. Subjects who discontinue study prior to C3D1 will not receive a second DEXA scan. An off study lean body mass/body composition DEXA scan should be performed at the End of Study Visit for any subject who completes visits at least through C3D1, but discontinues prior to the C5D1 DEXA.

[h] The EORTC QLQ-C30 (version 3) is a validated quality of life instrument for cancer patients. It consists of 30 items that encompass 3 symptom scales (pain, fatigue, nausea/vomiting), 6 single-item symptom items, 5 functional scales (physical, cognitive, role, emotional, and social), and one scale assessing global health status/quality of life. Each scale consists of 2-5 items. All items have four response categories (not at all, a little, quite a bit, very much), except for 2 items assessing overall health status/quality of life, which use a seven-point scale.

[i] Assessments can include CT or MRI, and whichever modality is chosen for the initial tumor assessment must be used for the week 8 assessment (Cycle 5 Day 1). Tumor measurements should ideally be obtained after DEXA scans for body composition. If standard of care scans are used, then there should be a 10-day washout after any CT scan with contrast prior to obtaining the DEXA scan. The choice of modality should be based primarily on the type of scan that the patient has previously received as their standard of care. Standard of care scans obtained within 28 days of C1D1 can be used as screening scans. Tumor measurements are to be performed on Cycle 5 Day 1 +/- 3 days.

[j] Following Cycle 6 Day 1, tumor measurements are to be repeated every 8 weeks (within 7 days prior to C9D1, C13D1, C17D1, etc.). Upon documented progression, confirmatory tumor measurements are to be repeated at 4 weeks +/- 3 days, for patients who elect to continue therapy until confirmation of progression.

[k] Tumor measurements should be performed, if possible, for subjects with clinical progression, to obtain radiographic restaging.

6. CORRELATIVE STUDIES

6.1 PHARMACOKINETICS (PK) SAMPLE COLLECTION

An enzyme-linked immunosorbent assay (ELISA) has been developed to specifically measure MABp1 levels in human plasma. Six milliliters of blood will be drawn into a single Na-Heparin treated tube at each PK collection time point (there are two collection time points at each infusion visit). These samples will be processed and plasma will be sent to a core laboratory for temporary storage, and will then be shipped to XBiotech in monthly batches for PK analysis. In addition to plasma levels of MABp1, these samples will be used to test for the presence of antibodies against MABp1, as well as baseline IL-1Ra levels.

Pharmacokinetics samples will be taken in all patients. The pharmacokinetics of MABp1 in plasma will be randomly analyzed. Plasma samples will also be randomly monitored for the development of anti-MABp1 antibodies. If the study meets the primary endpoint, then all samples will be tested in order to develop a population pharmacokinetic model.

7. CRITERIA FOR EVALUATION

7.1 SAFETY DATA MONITORING

Local labs for safety will be done prior to infusion. A 2nd sample will be taken and shipped to the central lab for analysis. Blinded lab and adverse event data will be reviewed at regular intervals by the Sponsor's Medical Safety Officer. Teleconferences will be held as needed between the Sponsor and the National Principal Investigator to discuss adverse events or any laboratory trends that develop. An independent data monitoring committee will also review unblinded safety and efficacy data at specified time points. See section 10, "Statistical Analysis", for a complete discussion.

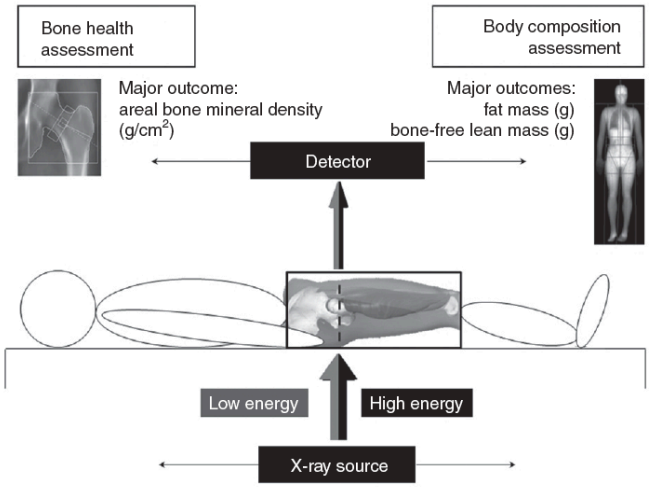
7.2 MEASUREMENT OF EFFECT

The difference in median overall survival between the MABp1 + BSC group will be compared to the placebo + BSC group. See section 10, "Statistical Analysis", for a complete discussion.

7.3 RADIOGRAPHIC ASSESSMENT OF BODY COMPOSITION

Dual energy X-ray absorptiometry (DEXA) is an X-ray imaging modality used to determine the mass of one material in the presence of another material, using the knowledge of their unique X-ray attenuation at different energies[36]. DEXA is an extremely accurate and precise method for measuring body composition, with a coefficient of variation for serial measurements of lean body mass between 0.4% and 1.3%[37].

Figure 7.1



This figure illustrates the basic principle of DEXA scanning. The X-ray beam is projected through the body, and the amount of attenuation by tissue compartment is measured by the detector (Toombs. Et al.).

DEXA scans will be performed at screening and at week 8 to assess changes in body composition. To qualify for inclusion, a site's DEXA should include the following compartments: **bone, fat, and lean**. Results are reported in grams, and should be reported for each extremity, trunk, head, and total, to allow for determination of an axial skeletal muscle index. Patients should be scanned with the **same DEXA machine using the same software version, at both screening and week 8.**

Investigative sites will be required to provide documentation of their scanners last calibration report by the manufacturer, as well as a QC reports that confirm that the scanner is still performing according to the manufacturer's specifications (i.e. scans of QC phantoms).

DEXA scans should not be performed if a patient has received intravenous or oral contrast within the previous 10 days.

7.4 QUALITY OF LIFE ASSESSMENT

Quality of life, including measurement of cancer related fatigue, will be assessed using the EORTC QLQ-C30 questionnaire (version 3). This questionnaire is a validated quality of life instrument for assessment of cancer related symptoms. It consists of 30 items that encompass 3 symptom scales (pain, fatigue, nausea/vomiting), 6 single-item symptom items, 5 functional scales (physical, cognitive, role, emotional, and social), and one scale assessing global health status/quality of life. Each scale consists of 2-5 items. All items have four response categories (not at all, a little, quite a bit, very much), except for 2 items assessing overall health status/quality of life, which use a seven-point scale.

The patient should complete the EORTC questionnaire without prompting from the site staff. After completion, the site staff will confirm that all questions have been answered prior to the patient leaving. If there are any incomplete items, the staff should request that the patient complete these prior to leaving this visit.

7.5 RADIOGRAPHIC MEASUREMENT OF TUMOR SIZE

Tumor response will be assessed by comparison of radiographic measurements of tumor size at baseline and measurements performed approximately every 8 weeks during study treatment and at specified time points following progression.

A Central Imaging Vendor will complete tumor measurements and only results of progression or stable disease will be reported back to the sites.

Definitions

Response and progression will be evaluated in this study using the Immune Related Response Criteria (irRC).

Measurable Disease

Index lesions: Must be accurately measured in two dimensions, with a minimum size of ≥10 x 10mm (two largest perpendicular diameters) by CT scan (CT scan slice thickness no greater than 5 mm) or 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Non-measurable Disease

All other lesions, including small lesions (longest diameter <10mm, <5x5 mm bidimensionally, or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Index and non-Index Lesions:

At the baseline (screening) tumor assessment, the dimensions of the two largest perpendicular diameters of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) will be measured and recorded. At the subsequent (week 10) tumor assessments, these measurements will be repeated, along with measurements of the two largest perpendicular diameters for any new, measurable lesions (≥10 x 10 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions).

Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed **as closely as possible** to the beginning of treatment and never more than 3 weeks (21 Days) before the beginning of the treatment (C1D1).

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Helical (or Spiral) CT and MRI. These techniques should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a ≤5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

7.5.1 Immune Related Response Criteria:

Evaluation of Target Lesions

Evaluation of radiographic response will be conducted using the Immune Related Response Criteria (irRC), as described by Wolchok, et al[60]. "For irRC, only index and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥10 x 10mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:"

Tumor Burden=$SPD_{\text{index lesions}}$ + $SPD_{\text{new, measurable lesions}}$

Complete Response (irCR): irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions). Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented.

Partial Response (irPR): irPR, decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation.

Progressive Disease (irPD): irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented.

- If a patient is classified as having irPD at a post-baseline tumor assessment, then confirmation of irPD by a second scan in the absence of rapid clinical deterioration is required. The definition of confirmation of progression represents an increase in tumor burden ≥25% compared with the nadir at two consecutive time points at least 4 weeks apart. **It is recommended that this be done at the discretion of the investigator because follow-up with observation alone may not be appropriate for patients with a rapid decline in performance status.**

Stable Disease (irSD): irSD, not meeting criteria for irCR or irPR, in absence of irPD.

Table 1. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Table 2. Derivation of irRC overall responses

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor burden),* %	**Non-index lesions**	**New, nonmeasurable lesions**	**Using irRC**
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25?	Any	Any	irPD†

*Decreases assessed relative to baseline, including measurable lesions only (>5 × 5 mm).
†Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

8. SAFETY AND TOLERABILITY

As of the last Development Safety Update Report, over 500 patients have been treated with Xilonix™ and over 2100 doses have been administered. The safety profile observed so far has been excellent. There have been no infusion reactions reported with the i.v. administration of the antibody (subjects are not pre-medicated with antihistamines or steroids) and there have been few injection site reactions reported with the subcutaneous formulation. These observations are highly consistent with the fact that there have been no human anti-human antibodies against Xilonix™ detected.

The adverse events reported vary by disease indication, but most of the events appear related to the underlying disease and there are no severe or serious toxicities that are obviously related to therapy with Xilonix™.

IL-1α is a key mediator of sterile inflammatory responses, however immunosuppression had been considered as a theoretical risk of the antibody. To date there is no evidence of immunosuppression or increased susceptibility to infection of any kind in patients treated with Xilonix™.

Platelets and other peripheral blood cells, including neutrophils and macrophages, may express IL-1α and thus may be targeted by Xilonix™. While there is no evidence that Xilonix™ induces antibody-directed cellular cytotoxicity, there may be the potential for Xilonix™ to cause thrombocytopenia, monocytopenia or neutropenia in some patients, however, this has not been observed to date.

An expanded discussion of potential risks and monitoring with Xilonix™ therapy is located in Section 4.6 of the Investigator's Brochure.

The following sections contain summary adverse event tables for two trials of Xilonix™ in patients with solid tumors. Summary tables for all trials in all indications using Xilonix™, as well as safety conclusions are located in sections 2.1-2.8 of the Investigator's Brochure.

8.1 ONCOLOGY (SOLID TUMOR) DATA:

The study 2009-PT004 was an open label, dose escalation trial of Xilonix™ in patients with advanced cancer. To be eligible, a patient was required to have metastatic disease that was refractory to all standard of care therapies. Patients at a single center in the US were dosed with 0.25, 0.75, 1.25 and 3.75 mg/kg of intravenous Xilonix™ every three weeks, and 3.75 mg/kg IV every two weeks. Phase 2 expansion cohorts were explored at the 2 highest doses. A total of 52 patients were treated, and >300 doses of Xilonix™ were administered.

Table 8.1: Summary of Adverse Events (Solid Tumor)

MedDRA Preferred Term (2009-PT004)	AEs by CTCAE Grade (% of total subjects, n=52)			
	Grade I-II	Grade III	Grade IV	Grade V
Fatigue	15 (28.8%)	2 (3.8%)	1 (1.9%)	0 (0.0%)
Proteinuria	12 (23.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	10 (19.2%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Edema peripheral	7 (13.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Constipation	6 (11.5%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Anorexia	6 (11.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspnea	6 (11.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperkalemia	6 (11.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	6 (11.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoalbuminemia	5 (9.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thrombocytopenia	4 (7.7%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Leukocytosis	4 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anemia	3 (5.8%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Diarrhea	3 (5.8%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Cough	3 (5.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Decreased appetite	3 (5.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Edema peripheral	3 (5.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperbilirubinemia	3 (5.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Myalgia	3 (5.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Transaminases increased	3 (5.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urinary tract infection	3 (5.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain	2 (3.8%)	2 (3.8%)	0 (0.0%)	0 (0.0%)
Headache	2 (3.8%)	1 (1.9%)	1 (1.9%)	0 (0.0%)
Aspartate aminotransferase increased	2 (3.8%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Lymphopenia	2 (3.8%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Pneumonia	2 (3.8%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Weakness	2 (3.8%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Blood alkaline phosphatase increased	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspepsia	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastroesophageal reflux disease	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypokalemia	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyponatremia	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neuropathy peripheral	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal failure acute	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Dyspnea	0 (0.0%)	2 (3.8%)	0 (0.0%)	0 (0.0%)

Delayed recovery from anesthesia	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Focal seizures	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Gastrointestinal hemorrhage	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Cramps Leg	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Disease progression	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Disease progression/death	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Ear pruritus	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Muscle Cramp	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)

Safety Conclusions

Adverse events observed in this trial were consistent with what would be expected in an advanced cancer population and there was no evidence that the antibody had any probable relation to AEs of any kind. The most common AE was proteinuria, and 4 of 12 events were grade II (2+) as measured by urine dipstick. Two of these patients, however, had ureteral stents and a large amount of blood (3+) in urinalysis; one had proteinuria performed just prior to the first infusion, and the last one had a history of proteinuria for 6 months prior to entering the study. The remaining 7 (17%) patients had grade I (1+) proteinuria, which correlates poorly with confirmed microalbuminuria[38]. The majority of these patients had previously been treated with Avastin as well. A randomized trial will clarify whether or not proteinuria is an actual consequence of Xilonix™ therapy.

The following table shows safety data from V2.4 of the PT023 trial. This version of the trial enrolled patients with metastatic colorectal cancer and concomitant cachexia (>5% weight loss in previous 6 months). Patients were randomized 1:1 to receive Xilonix™ + best supportive care versus megestrol acetate + best supportive care. Best supportive care included 3+ line chemotherapies, such as cetuximab or regorafenib. Adverse events are presented for both the Xilonix™ (N=20) and megestrol (N=20) arms. This data is preliminary as patients are still on study, and the data is still undergoing monitoring and cleaning.

Table 8.2: Summary of Xilonix™ AEs (CRC with Cachexia)

MedDRA Preferred Term (2012-PT023; MABp1 Arm)	AEs by CTCAE Grade (% of total subjects, n=20)			
	Grade I-II	Grade III	Grade IV	Grade V
Nausea	7 (35.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	7 (35.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abdominal pain	5 (25.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)
Fatigue	5 (25.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)
Diarrhea	4 (20.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Chills	3 (15.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Alopecia	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Back pain	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Constipation	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Dehydration	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dizziness	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Edema limbs	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Palmar-plantar erythrodysaesthesia syndrome	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ascites	1 (5.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)
Chest pain - cardiac	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Dyspnea	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Acidosis	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Alkaline phosphatase increased	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anemia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anorexia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anxiety	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood and lymphatic system disorders	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood bilirubin increased	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Confusion	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cough	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Creatinine increased	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dysgeusia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Endocrine disorders	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ERYTHRODYSESTHESIA	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fall	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fecal incontinence	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fever	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gait disturbance	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoalbuminemia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyponatremia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Laryngeal hemorrhage	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorder	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neck pain	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neutropenia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Palpitations	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sinus disorder	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin hyperpigmentation	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Somnolence	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stomach pain	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Upper respiratory infection	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urinary incontinence	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Weight loss	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Wheezing	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Small intestinal obstruction	0 (0.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)
Bone pain	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Hyperglycemia	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Hypotension	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)
Upper gastrointestinal hemorrhage	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)

Table 8.3: Summary of Megace AEs (CRC with Cachexia)

MedDRA Preferred Term (2012-PT023; Megestrol Arm)	AEs by CTCAE Grade (% of total subjects, n=20)			
	Grade I-II	Grade III	Grade IV	Grade V
Dyspnea	5 (25.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Fatigue	4 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension	3 (15.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Back pain	3 (15.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urinary tract infection	3 (15.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diarrhea	2 (10.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Constipation	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cough	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastroesophageal reflux disease	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Headache	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Palmar-plantar erythrodysaesthesia syndrome	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abdominal pain	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acute kidney injury	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Alopecia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anemia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bronchial infection	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bruising	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dry skin	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema multiforme	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fall	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haematochezia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hoarseness	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypokalemia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoxia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Insomnia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mucositis oral	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorder	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non cardiac chest pain	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral sensory neuropathy	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prostate infection	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rectal pain	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sinus Tachycardia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Skin infection	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sore throat	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Spasticity	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tumor pain	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vomiting	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Weight gain	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypovolaemia	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperglycemia	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Leukocytosis	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Thromboembolic event	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Obstruction gastric	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
Disease progression	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)

At this point there have been no adverse trends identified in this study. The adverse events reported appear to be related to the underlying disease, or related to concomitant chemotherapy.

8.2 REFERENCE SAFETY INFORMATION: POTENTIAL ADVERSE REACTIONS

Over 500 patients have been treated using Xilonix in patients with advanced solid tumors, advanced hematologic malignancies, metastatic colorectal cancer, peripheral vascular disease, type II diabetes, acne vulgaris, plaque psoriasis, and pyoderma gangrenosum. Over 1200 doses of Xilonix were administered at 7.5 mg/kg to refractory, metastatic CRC patients with cancer associated symptoms at baseline (ECOG performance status 1 and 2). In this trial (PT026), which is the largest controlled trial completed with Xilonix to date (N=309), patients were dosed at 7.5 mg/kg for metastatic colorectal cancer. The most common AEs reported (>10%) were abdominal pain, peripheral edema, fatigue, anemia, constipation, decrease in weight, asthenia, decreased appetite, and nausea. The majority of these events were grade 1 or 2, and appeared to be related to the underlying CRC. The prevalence of these events was similar in the Xilonix and placebo groups. Two infusion reactions were reported in this trial, and they were not serious or severe (grade I or II).

The RSI has been updated based upon data from a randomized, double-blind, placebo controlled trial in metastatic colorectal cancer (2014-PT026), which was recently completed. In this trial, there was no difference in the incidence of thrombocytopenia, proteinuria, nausea, or diarrhea, between the two groups; therefore these terms were removed from the list of expected adverse reactions (ARs). There were two infusion reactions that occurred in the PT026 trial, as well as one infusion reaction reported as an SAE in the PT023 trial.

The mechanism behind infusion reactions is not clear in all cases. It may involve a reaction against the antibody products themselves, or, against some minor residual component from the manufacturing process (i.e. host cell proteins). To date, after administration to over 500 patients, and over 3000 doses, the risk of infusion reaction remains extremely low.

For the purposes of expedited safety reporting in clinical trials, the following should be considered expected events:

- **Infusion Related Reactions**

Refer to Section 4.6 of the Investigator's Brochure for clinical trial summaries of Xilonix, and Section 5 for a Summary of Data and Guidance for the Investigator.

8.3 Overall Risk and Benefit Assessment

Chemotherapy and radiotherapy in the context of advanced metastatic or unresectable colorectal cancer is largely palliative—meaning that complete eradication of the tumor is not expected. The primary goal in this setting is reducing symptomatic effects of the tumor for as long as possible. Due to toxicity, however, these treatment modalities are poorly suited for this objective. Even with the most recent agents (such as multi-kinase inhibitors) treatment related morbidity often results in discontinuation of therapies— ultimately leading to uncontrolled progression and death. New agents that exhibit anti- neoplastic activity and provide improvement in tumor related symptoms are vitally needed to treat this and other advanced cancer populations.

Specific antagonism of IL-1α through Xilonix™ therapy is viewed as a unique, broad acting tumor suppression strategy that encompasses significant activity to ameliorate symptoms associated with the disease, as well as improve overall survival. IL-1α is unique in its involvement in so many processes related to tumor progression and collateral symptomatic effects of malignancy. The excellent safety and tolerability profile of the agent make it an ideal treatment option in advanced stage disease, particularly where the use of cytotoxic or other therapies with considerable toxicity are not supported by the risk benefit profile.

Blocking IL-1α appears to normalize the metabolic energy balance with the net accumulation of lean body mass (LBM). An average LBM increase of 1.9±2kg was seen in 70% of patients treated ($p<0.001$) compared to their baseline values. These same patients had improvements in pain, anorexia, and fatigue as measured by the EORTC- QLQ-C30. Traditional, radiographic evidence of anti-tumor activity was also noted, with 21% of patients having stable disease for 3 months or greater, including a partial response in a patient with metastatic colorectal cancer. Additionally, colorectal cancer patients with improvements in LBM had a trend towards a clinically significant overall survival benefit.

For this agent, this reversal of tumor related symptoms, is viewed as the direct result of an anti-neoplastic mechanism of action and is potentially a more powerful surrogate for clinical benefit than traditional radiographic based assessments.. In the tumor microenvironment IL-1α driven sterile inflammation results in neoangiogenesis and tissue matrix remodelling both of which are critical for tumor growth. Within the vascular space, membrane associated IL-1α on PBMCs and platelets activate vascular endothelium, which in turn leads to upregulation of adhesion molecules and further infiltration of the microenvironment by pro-tumor inflammatory cells. Activation of the vascular endothelium also provides a mechanism by which tumor cells (in the form of tumor-platelet microemboli) can escape into new areas of metastasis.

The importance of IL-1α to tumor growth and invasiveness has been illustrated in numerous pre-clinical models, as well as from studies examining biopsies of multiple tumor types. However, the most compelling evidence to date is that illustrated in our pilot oncology trial, 2009-PT004.

Radiographic evidence of tumor regression has been observed in some cases, and multiple patients have experienced prolonged stable disease. Adverse events observed in these oncology patients have been mild, with 97% being grade 2 or lower in severity. These events have also shown no obvious relation to study drug administration.
Xilonix is a non-toxic, anti-neoplastic agent that has shown preliminary evidence of improving both metabolic and functional symptoms in patients who have exhausted all lines of anti-tumor therapy. The demonstration of LBM increases in advanced stage patients with a non-anabolic agent could represent a significant milestone in the management of metastatic cancer, as well as a novel surrogate for anti-neoplastic activity in refractory patients. Based upon these observations, the risk benefit analysis of Xilonix appears to be favourable and this therapy should be explored further advanced cancer patients.

9. ADVERSE EVENTS

9.1 DEFINITION OF ADVERSE EVENT (AE)

An adverse event is defined as any new or worsening untoward medical occurrence in a subject participating in a clinical study that does not necessarily have a causal relationship with the pharmaceutical or biological agent under study. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including laboratory findings), symptom, or disease temporally associated with the use of MABp1, whether or not it is apparently related to MABp1
- A concurrent illness
- An exacerbation, or an unexpected increase in frequency or intensity of a preexisting condition, including intermittent or episodic conditions.
- A significant or unexpected worsening of the condition/indication under investigation. However, anticipated day-to-day fluctuations or non-serious, expected progression of the disease under investigation (based upon the Investigator's clinical judgment) are not to be considered AEs
- A suspected interaction between the investigational drug and concomitant medications
- Any clinically significant laboratory abnormality (including radiological interpretations, histopathological findings, etc.)

9.2 DEFINITION OF SERIOUS ADVERSE EVENT (SAE)

A serious adverse event is defined as any untoward medical occurrence that meets any of the following criteria:

- Results in death
- Life-threatening
- Requires or prolongs inpatient hospitalization
- Results in a persistent or significant disability or incapacity
- Congenital anomaly/birth defect or
- An important medical event that, while it may not result in death or be immediately life-threatening or require/prolong hospitalization, may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above. 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 the development of drug dependency or drug abuse.

Note that seriousness and severity should not be confused. A subject could experience a severe headache that would not qualify as an SAE, while another might experience a mild stroke that, while not severe, would be considered serious.

9.3 RECORDING OF ADVERSE EVENTS

All untoward events occurring between Cycle 1 Day 1 and 30 days following the last administration of the investigational drug must be recorded on the eCRF, regardless of whether they are considered related to study drug or not.

All AEs should be recorded in a standard medical terminology as concisely as possible. The AE recorded should not be a procedure or a clinical/laboratory measurement, but should reflect the event leading to the procedure or the cause of the clinical/laboratory abnormality, if known.

Whenever possible, AEs should be evaluated and recorded as a diagnosis, rather than individual signs and symptoms. However if a definitive diagnosis is not possible, the individual signs and symptoms should be recorded. Any AE that worsens in intensity, or becomes serious, should be recorded as a new event.

9.4 EVALUATING ADVERSE EVENTS

All AEs will be graded according to the CTCAE version 4.0.

9.5 ASSESSMENT OF CAUSALITY

Investigators are required to assess the relationship, if any, of each AE or SAE to the investigational drug using clinical judgment to determine the degree of certainty with which an AE can be attributed to the investigational drug. Alternative causes, such as natural history of the underlying disease, other risk factors, and the temporal relationship of the event to the administration of the study medication must be considered.

Relationship to study drug is summarized as follows:

- **Not Related:** There is another obvious cause of the AE
- **Unlikely to be related:** There is another more likely cause of the AE
- **Possibly related:** The AE could have been due to the investigational drug
- **Probably related:** The AE is probably attributable to the investigational drug
- **Definitely related:** The AE is most likely attributable to the investigational drug

9.6 REPORTING REQUIREMENTS

All serious adverse events (SAEs) should be reported to the Sponsor within 24 hours of knowledge of the event. These immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The Investigator should also submit SAEs to the IRB/EC according to their IRB/EC guidelines [ICH-GCP E6]. Drug-related Serious Adverse Events will be reported to the FDA by XBiotech’s Medical Safety Officer according .32.

9.7 SAFETY LEAD IN PLAN

In order to more accurately characterize the adverse event profile at the 7.5 mg/kg dose level, the Sponsor will conduct a blinded review of adverse event data for the first 10+10 patients enrolled on this protocol at that dose level. Review of the data will occur after completion of 2 cycles (28 days) of therapy for the first 10 patients, and then again after the second 10 patients. As there is a 2:1 randomization, approximately 6 of the first 10 and 13 of the first 20 patients will have received Xilonix™. A report of the adverse event data at each of these two time points will be submitted to the FDA within 10 days of the last patient’s completion of 2 cycles.

The Sponsor will voluntarily suspend enrollment on the study, immediately and at any time upon review of safety data during the lead in period, if ≥ 33% (≥ 6) of patients have experienced a dose limiting toxicity (DLT). In this event, enrollment will be suspended pending further IDMC review and pending further guidance from the FDA. Under these circumstances, the IDMC will be asked to review un-blinded data and make a recommendation regarding the safety of the dose level in this population.

A DLT will be defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications occurring during the first two cycles (i.e. 28 days) of therapy, with relationship to study drug determined as possible, probable, or definite and meeting the criteria as Grade 3 or Greater Hematological or Non-Hematological Toxicity as assessed by the CTCAE V4.0.

10. STATISTICAL ANALYSIS

10.1 STUDY DESIGN

This will be a double blind, randomized, placebo controlled, multicenter, parallel-group Phase III trial comparing the efficacy and safety of Xilonix™ plus best supportive care (BSC) to placebo plus BSC. Consented eligible subjects will be enrolled and randomly assigned to treatment arm or placebo arm with 2:1 ratio respectively. Subjects randomized to treatment arm will receive Xilonix™ and those in control arm will receive placebo via intravenous infusion every 2 weeks (one cycle) plus BSC. Total study duration will be 18 months. An Independent Data Monitoring Committee will be formed prior to the study initiation to monitor the safety during study, as well as to evaluate the efficacy and safety results at the time of the protocol-specified interim analysis.

10.2 STUDY ENDPOINTS

10.2.1 Primary Efficacy Endpoint:

Overall survival (OS) will be the primary endpoint of this study survival time will be defined as the duration from the date of randomization until death. Subjects who are alive at the end of follow-up will be censored and survival time will be defined as time from randomization to censor date. The overall survival between the Xilonix™ + BSC group and placebo + BSC group will be compared using an unadjusted log-rank test.

10.2.2 Secondary Endpoints:

Secondary efficacy variables will include change in lean body mass (LBM) measured by dual-energy X-ray absorptiometry (DEXA) scans, change in Quality of Life assessed through the cancer-specific EORTC QLQ-C30 questionnaire, stabilization of platelet counts, progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR).

10.2.3 Exploratory Endpoint:

Clinical Response Rate (CRR) will be the exploratory endpoint for this study. This will be a composite measure assessing the change in LBM, fatigue, pain, and appetite from baseline to week 8. Clinical response will be defined as, 1) Improvement or stabilization (≥0 kg change) of LBM as assessed by DEXA scan, and 2) Improvement or no worsening (≤0 score point change; low scores reflect better functioning and lower symptom distress) on any two of the three symptom scale measures (fatigue, pain, appetite) of EORTC QLQ-C30. Patients missing the follow-up assessment will be considered non-responders.

10.2.4 Safety Endpoint:

Safety endpoints will be evaluated by monitoring adverse events from clinical and laboratory reporting. Adverse events will be classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). Significant trends in the distribution and severity of the adverse events across the study groups will be assessed.

10.3 SAMPLE SIZE AND POWER

Prior research has reported a median survival of 4.6 months among refractory, metastatic colorectal cancer patients with BSC in a comparable patient cohort. On the other hand, as observed in the colorectal cancer cohort of our phase I/II trial, the median survival was 6.7 months for all enrolled colorectal cancer patients and 8.7 months for the per-protocol population. Using a conservative approach, the current study is designed to detect at least 30% improvement in median OS in treatment arm (6.0 months, hazard rate in treatment arm (h1)=0.116)) compared to the control arm (4.6 month, hazard rate in control arm (h0)=0.151)). We propose to test the null hypothesis for hazard ratio (h1/h0) =1 and alternative hazard ratio ≤ 0.767. With a 2:1 allocation ratio and 5% oversampling, a total of 600 subjects (400 and 200 in treatment and control arm respectively) will be required to detect the 30% increase in median survival (from 4.6 to 6.0 months, hazard ratio 0.767) with one-sided Type I error probability (alpha) of 0.025, and 80% power (1-beta=0.80). The total number of 552 deaths during the 18 month follow-up in the overall study population will provide the above power. The survival curves will be estimated with the Kaplan–Meier method and compared for statistical significance by log-rank test.

In contrast to a fixed-sample trial, where the data is analyzed at end of the study, we propose a group sequential design that provides for interim analyses before completion of trial while maintaining the specified overall Type I and Type II error probabilities.

The trial will have three stages (two interim, one final). As determined based on alpha spending function of O'Brien and Fleming sequential group design (O'Brien PC, Fleming TR, 1979), survival analyses will be performed after 276 (50%), 414 (75%) and 552 (100%) deaths at the respective stages. The efficacy and futility stopping boundaries will be computed separately.

The criteria for the early termination for efficacy (rejection of null hypothesis) or to accept the null hypothesis will be based on the group sequential design. If the test statistics crosses the pre-specified boundaries for type I error (0.0029, 0.010, and 0.012; cumulative alpha of 0.0029, 0.013, and 0.025 respectively) the trial will stop for efficacy. Otherwise, the trial continues to the next stage. The beta levels for stopping the trial for accepting the null hypothesis will be included in the detailed statistical analysis plan for the Independent Data Monitoring Committee (IDMC).

If efficacy is established at an interim analysis, enrollment will be stopped and the control group will be allowed to crossover. All subjects will be followed up until death, loss to follow-up, or termination of the study.

Randomization Strategy:

A central randomization scheme with Interactive Web Response System (IWRS) will be employed to facilitate effective randomization and allocation concealment. The scheme will involve a block randomization technique, randomly assigning participants within blocks based on a 2:1 allocation ratio. The randomization sequence will be generated using Oracle Clinical Remote Data Capture application (Oracle Corporation, Redwood City, CA, USA).

10.4 STATISTICAL ANALYSIS PLAN

The primary efficacy analysis will be conducted for the intent-to-treat (ITT) and Per-protocol (PP) population. The ITT population will consist of all randomized patients. The PP population will be defined as those patients in the ITT set who are compliant with the study protocol.

Given the nature of change to the study design, patients enrolled prior to modification (V3.0) will be excluded from the primary efficacy analysis. Those patients will be analyzed separately.

Patient Characteristics and Baseline Comparisons:

The ITT population will be included for analysis of demographic and baseline findings. Data will be summarized for each treatment group, i.e. Xilonix™ and placebo arm. Descriptive analysis will be performed summarizing age, gender, Eastern Cooperative Oncology Group (ECOG) status, co-morbidities, cancer therapy, and other relevant baseline risk factors by treatment group. Baseline biochemistry, hematology data will be summarized in separate tables. Continuous variables will be reported as mean ± standard deviation (SD), median and inter-quartile range (IQR) for non-normal data. The categorical variables will be reported as number of cases (n) and percentage. The baseline characteristics will be compared across the groups for overall difference by using independent-samples t-test for continuous variables and chi-square test (Fisher's exact if n <20) for categorical data. Normality of the analysis variables will be tested using Shapiro-Wilks test. If the Shapiro-Wilks test is significant, continuous data will be compared using Wilcoxon (for paired data) and Mann-Whitney nonparametric test. Correlation between parameters was evaluated using Spearmann correlation coefficients. A two-tailed p value of <0.05 will be considered statistically significant for the descriptive summary statistics.

Efficacy Evaluation: Primary Efficacy Endpoint

Subjects who are alive at the analysis time point the will be censored, and survival time will be defined as time from randomization to censor date. Patients, who are lost to follow-up or discontinued, will be censored at time of last contact. A censoring variable will be created identifying censored observation. The primary endpoint, overall survival, will be summarized by Kaplan-Meier method and compared between the treatment groups using un-adjusted log-rank test. The median survival, cumulative survival probability and 95% confidence interval (CI), calculate by log-log transformation and 25^{th} and 75^{th} percentiles, will be reported according to treatment groups. Kaplan-Meier curves will be generated plotting the survival probability and probability of occurrence in time. Number of patients at risk on various time intervals will be presented on the curve. The type I error rate to be used for determining statistical significance of the primary outcome is defined in section 10.3 "interim efficacy analyses".

A secondary supportive analysis will be performed comparing survival probability across treatment groups, stratified by age (dichotomizing by median), gender, ECOG performance status, KRAS mutation status, regorafenib and bevacizumab treatment failure status, and number of prior antineoplastic therapies. Survival probability and 95% CI for treatment groups will be reported for by each stratum.

A multivariate Cox proportional hazards regression (CPH) method will be used for assessing independent predictors of OS after adjusting for potential confounders. Selection of covariates will primarily be based on a priori knowledge, and include age (continuous scale), prior cancer therapy (number of regimens will be entered on continuous scale), ECOG performance status (categorical 0-1, 2), baseline IL-1 RA level and KRAS mutation status (coded as no=0, yes=1), and baseline body weight (continuous scale). A backward selection method will be used for variable selection; the p-value threshold will be set at 0.10. Proportional-hazard assumption will be tested by Schoenfeld residual analysis. The hazard ratio (HR) and 95% CI will be computed and presented in the results. The CPH analysis will be exploratory in nature. Receiver operating characteristic (ROC) analysis will be performed to identify the optimal cut-off of baseline IL-RA level that best discriminate overall survival.

Efficacy Evaluation: Secondary Efficacy Measures

Secondary endpoints, QoL score and LBM will be evaluated for the absolute change at 8 week follow-up on each measure, as well as through a responder analysis comparing objective response rate across study arms.

LBM: Patients showing stabilization or improvement from baseline (≥0 kg change) will be considered LBM responders. Patients experiencing LBM reduction will be defined as non-responders. Those not having a second evaluation for going off the study or any other reason, will be considered non-responder. Responder rate will be compared using Pearson chi-square test. Proportion by group, relative risk and odds ratio estimates will be presented with 95% confidence intervals (95% CI).

Absolute change will be compared between the Xilonix™ and placebo group using analysis of covariance (ANCOVA) method (SAS GLM procedure) with treatment groups as factor and baseline value as covariate. The difference in least-square means and 2-sided P values will be derived from analysis of covariance model for comparison.

EORTC: The EORTC survey results will be converted to domain specific scores using the prescribed algorithm. And scores on EORTC QLQ-C30 functional and symptom scales will be summarized according the randomization groups. Score on each scale will be summarized by study arms.

Patients showing stabilization or improvement from baseline (≤0 change) on any two of the three symptom scales (pain, fatigue, appetite) will be considered responders. Patients experiencing reduction or worsening will be defined as non-responders. The comparison of responder rate and absolute change will performed similar to as described for LBM.

Platelet Count: Change in platelet count from baseline to follow-up will be compared between treatment groups using the analysis of covariance method described above. The last visit cycle where at least 20 patients per group are on study will be used for follow-up data cut-off for this measure. Trend line plots displaying the median platelet count over time (visit cycles) by treatment groups will be generated..

Progression Free Survival (PFS): This will be defined as time from randomization to tumor progression or death. Patients surviving without disease progression at end of study will be censored. PFS will be compared by Kaplan-Meier method using log-rank test. Kaplan-Meier plots by treatment arm will be produced, and point estimates and 95% CIs will be summarized.

Objective Response Rate (ORR): The ORR will be estimated by dividing the total number of confirmed complete response (CR) and partial response (PR) by the total number of patients randomized. Exact 95% confidence intervals for the response rate in each treatment arm will be calculated. Best overall response (BOR), determined from the sequence of cycle responses assessed, will be used for analysis purposes. Response rates will be compared between treatment groups using a Pearson Chi-square test and Wald 95% CI will be reported.

Disease Control Rate (DCR): The DCR will be estimated by dividing the total number of confirmed CRs, PRs and stable disease (SD) by the total number of patients randomized. DCR

will be analyzed as described for RR. Best overall response (BOR), will be used for DCR analysis. Proportion of response category by group along with 95% CI will be reported.

Inferential analysis for the secondary endpoints, without multiplicity correction, will be carried out for stratification variables (age, prior therapy, ECOG performance status, KRAS mutation status, Regorafenib and bevacizumab failure status), One-way ANOVA, and Fisher's exact tests will be used to compare differences across stratification groups. Proportion by group along with 95% CI will be reported.

A two-tailed p value of <0.05 will be considered statistically significant for all secondary endpoints. SAS 9.2 or higher (SAS Institute Inc., Cary, NC) will be used for statistical analysis.

11. STUDY MANAGEMENT AND ADMINISTRATION

11.1 ETHICAL CONDUCT OF STUDY (GCP)

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (48th General Assembly, Somerset West, Republic of South Africa, October 1996), the guidelines of ICH GCP (CPMP/ICH/135/95), as well as the demands of national drug and data protection laws and other applicable regulatory requirements, will be strictly followed. Approval will be obtained from the appropriate regulatory authorities before sites are initiated.

11.2 IRB AND ETHICS COMMITTEE APPROVAL

Prior to initiation of the study, the protocol, the informed consent form, the subject information sheet(s), details of the subject recruitment procedures and any other relevant study documentation will be submitted to the responsible IRB or Ethics Committee (EC). The Investigator will report promptly to the IRB/EC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/EC annually, or more frequently if requested by the IRB/EC. Upon completion of the study, the Investigator will provide the IRB/EC with a brief report of the outcome of the study, if required.

11.3 PROTOCOL MODIFICATIONS

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The IRB/EC must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented. The Investigator must not implement any deviation from or change to the protocol, without discussion with, and agreement by, the study Sponsor and prior review and documented approval/favorable opinion of the amendment from the relevant IRB/EC, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in CRA(s), change of telephone number(s)). Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

11.4 SUBJECT INFORMATION AND CONSENT

The Investigator is responsible for ensuring that no subject will receive any study-related examination or activity before that subject has given an IRB/EC approved informed consent. The subject must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the subject. The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview, the subject may be given time to reflect if this is required, or if the subject requests more time. Subjects and/or legal guardian forms will be kept and archived by the Investigator in the Investigator's study file. It should be emphasized that the subject is at liberty to withdraw their consent to participate at any time, without penalty or loss of

benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact their subsequent care. The Investigator will notify in writing each subject's primary care physician (or equivalent) of the subject's intent to participate in the study.

11.5 DATA PROTECTION AND CONFIDENTIALITY

In signing the final protocol, every participating Investigator agrees to keep all information and results concerning the study and the investigational product confidential. The confidentiality obligation applies to all personnel involved at the investigational site. The Investigator must ensure that each participant's anonymity will be maintained in accordance with applicable laws. On eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their name, but by subject ID number. The Investigator should keep a separate log of ID numbers, names and addresses. Documents that contain the names associated with these ID numbers (e.g. written consent/assent forms), are not for submission to the Sponsor and should be maintained by the Investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, auditing or monitoring by the Institutional Review Board/EC, the Sponsor personnel or their affiliates and designees (such as CRAs).

Copies of radiological scans and autopsy reports (and other documents) that may be requested by the Sponsor should be de-identified. The Investigator shall obtain all such permissions and authorizations as may be necessary or desirable to allow the collection and use of information protected under federal privacy laws and state privacy laws, including permission/authorization for monitoring and analysis (including re-analysis in combination with results of other studies), for regulatory submission purposes and for applicable reporting (if any) required to be made by Sponsor, its affiliates and their designee.

11.6 STUDY REPORT AND PUBLICATIONS

A final integrated clinical/statistical report will be prepared that is compliant with the ICH Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95). The results of this study will be published and/or presented at scientific meetings in a timely manner. The publication policy is described in the contract between the Sponsor and Investigator.

11.7 STUDY FILES AND RETENTION OF RECORDS

Copies of all study documents should be retained by the Investigator until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product, in accordance with 21 CFR 312.62. These documents should be retained for a longer period however, if required by regulatory requirements or by agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The final database will be archived according to the regulatory requirements.

11.8 CASE REPORT FORMS

Data for this protocol will be captured electronically in an Electronic Data Capture (EDC) system. Designated study personnel will be provided unique user names and passwords. Each study personnel will have specific access within the electronic data collection system based on

their role. The EDC system contains an audit trail associated with each individual's unique password that will document date and time of data entry and revisions. All protocol-specified data is to be entered into the EDC system in a timely manner for review and audit by XBiotech USA, Inc. All data is to be entered such that it will allow accurate interpretation and tabulation. It is the Investigator's responsibility to ensure that all discontinued orders or changes in study or other medications entered into the database correspond to entries in the subject's medical records (i.e. source documents) and to acknowledge accurate completion of the eCRF.

11.9 DRUG ACCOUNTABILITY

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

- Initial inventory upon receipt of supplies at the study site
- Identification number of each subject to whom test drug was administered
- Date(s), quantities, lot numbers and calculations for all test drugs administered
- Final inventory (upon completion of the study)

This inventory must be available for inspection by the Clinical Research Associate. The Investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study medication to the study site, the inventory at the site, the usage for each subject, and destruction. The inventory must be available for monitoring, auditing or inspection. A drug dispensing log must be kept current and should contain the following information:

- The subject identification number to whom the drug is dispensed
- The lot number of the drug dispensed
- The date(s) and the quantity of the drug dispensed to the subject

11.10 INSPECTIONS

Investigator sites, the study database and study documentation may be subject to quality assurance audits during the course of the study either by the Sponsor or their appointed representatives. In addition, regulatory bodies at their discretion may conduct inspections. The Investigator shall permit the authorized Sponsor, agents of the Sponsor, and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all records relating to an investigation, including subject records. The Sponsor will not, however, copy any source data from the patient’s dossier. Completed eCRFs must be made available by the Investigator for review by the Sponsor, agents of the Sponsor, the CRA and the regulatory agencies. To ensure the accuracy of data submitted, it is mandatory that representatives of the Sponsor and of the regulatory agencies have direct access to source documents (e.g. subject medical records, charts, laboratory reports, etc.). Subject confidentiality will be protected at all times.

11.11 ACCESS TO INFORMATION FOR MONITORING

CRAs will establish and maintain regular contact between the Investigator and the Sponsor. CRAs will evaluate the competence of each study center, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, CRAs will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. CRAs are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. CRAs will

also monitor adherence to the protocol at the Investigator site. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained. The CRA will make written reports to the Sponsor on each occasion when contact with the Investigator is made, regardless of whether it is by phone or in person. During monitoring visits, entries in the eCRFs will be compared with the original source documents. The Investigator must agree to meet with the CRA at regular intervals and to cooperate in resolving any queries or findings made during the monitoring process.

11.12 STUDY DISCONTINUATION

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/EC will also be promptly informed and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

APPENDIX A

Eastern Cooperative Oncology Group (ECOG) Grades	
Grade	**ECOG**
0	Fully Active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.,* light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

APPENDIX B

EORTC-QLQ-C30 (version 3) appended

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you providewill remain strictly confidential.

Please fill in your initials: **aaaa**
Your birthdate (Day, Month, Year): **bdbdbccd**
Today's date (Day, Month, Year): 31 **bdbdbccd**

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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