Women's Triple-Negative First-Line Study: A Phase II Trial of Panitumumab, Carboplatin and Paclitaxel (PaCT) in Patients with Localized Triple-Negative Breast Cancer (TNBC) with Tumors Predicted Insensitive to Standard Neoadjuvant Chemotherapy

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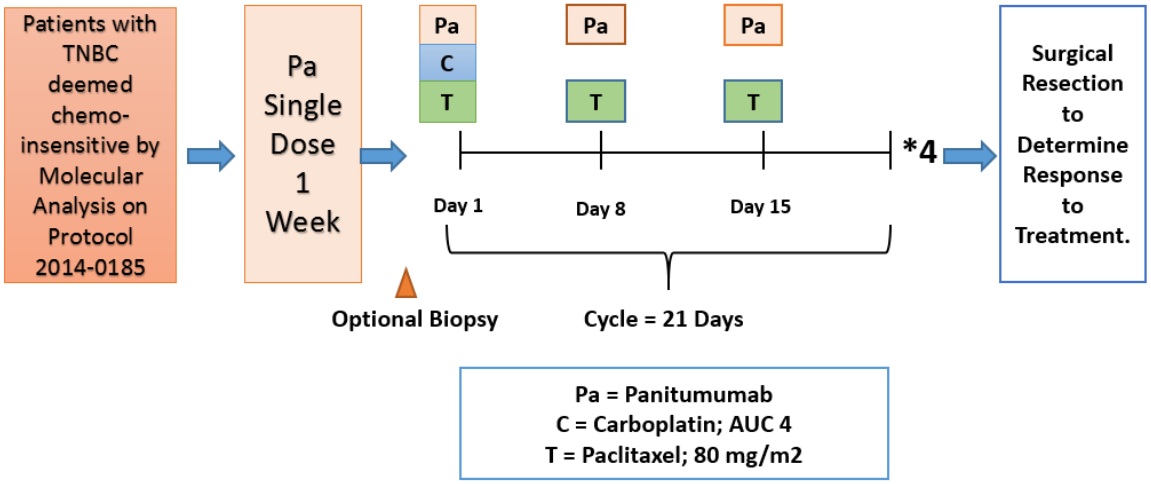
1.0 Study Schema:



* Patients will undergo a planned 4 cycles of therapy prior to surgical resection.

2.1 Introduction

Patients with localized TNBC are preferably treated with systemic chemotherapy in the neoadjuvant setting (NACT) as this allows for close monitoring of response in the intact primary tumor and often results in 'down-staging' of tumors, which increases the feasibility of breast conserving surgery. The response to NACT at the time of surgical resection can be determined by measuring the amount of residual cancer remaining in the breast and draining lymph nodes during routine pathologic evaluation and is such a powerful indicator of prognosis that the Food and Drug Administration (FDA) has recognized significant improvement in complete response to neoadjuvant therapy as a pathway to drug approval. Investigators at MDACC have developed and validated a scoring system known as the Residual Cancer Burden (RCB) to quantify the extent of residual disease remaining after NACT and surgical resection.[2] Approximately 50% of patients with localized TNBC treated with standard taxane/anthracycline-based NACT will have either pathologic compete response (pCR/RCB-0) or minimal residual disease (RCB-I) at the time of surgical resection and those patients have identical and exceptionally good long -term prognosis. Unfortunately, those with more extensive residual disease (RCB-II or RCB-III) have a much worse prognosis, with 50%-80% of patients developing distant metastatic disease within 3 years of initial diagnosis.[3] Additionally, clinical trials of NACT in breast cancer have demonstrated that patients without response to their first chemotherapeutic regimen have very low chance (5%) of achieving pCR after their second neoadjuvant chemotherapy regimen.[4] However, this has not been the case with targeted regimens such as trastuzumab in HER2+ tumors, suggesting that intrinsic resistance to chemotherapy can be overcome with appropriate targeted therapy.[5] Though several targeted agents have been tested for treatment in TNBC, so far none have been successful. The underlying causes of this failure are commonly attributed to the molecular heterogeneity of tumors classified within the 'catch all' category of TNBC as well as the dilution effects of chemotherapy sensitive disease which requires clinical trials to enroll larger number of patients to show benefit of combined targeted therapy/chemotherapy regimens over standard chemotherapy. Additionally, clonal selection of resistant cells with escape mechanisms also likely develops.

Recent advances in gene expression profiling have identified subgroups of triple-negative breast cancer (TNBC) with distinct molecular features that, if appropriately selected, may be more responsive to targeted therapy with existing FDA-approved drugs, leading to rapid improvement of outcomes in this high-risk breast cancer population.[1,6-8]

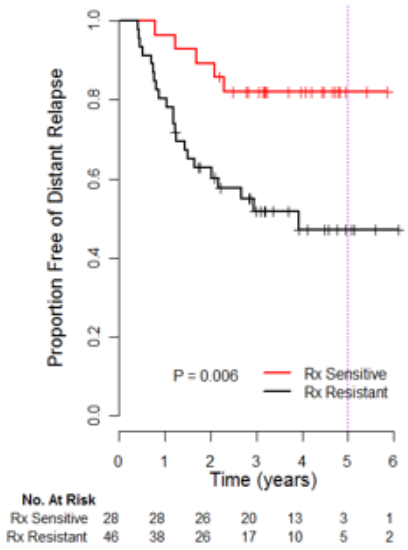


Fig 1: Distant RFS by genomic prediction of chemo-sensitivity in ER-/HER2- breast cancer

<u>Prediction of chemosensitivity and molecular aberrations associated with TNBC subtypes:</u> Our collaborator, Dr. Symmans, and his team have developed microarray-based predictive signatures chemotherapy response using fresh primary tumor tissue obtained from a routine biopsy of breast cancer at the time of diagnosis or surgery. This approach has been retrospectively validated and tested for feasibility using a prospective registry study(MDACC clinical trial 2011-0007).[9] The proposed predictor was tested on an independent cohort of breast cancers irrespective of receptor status (N=198, 99% with clinical Stage II-III) who received neoadjuvant (N=180) or adjuvant (N=18) taxane-anthracycline chemotherapy. Predictions were accurate if ER+/HER2- (30% predicted sensitive, DRFS 97%, CI 91-100; ARR 11%, CI 0.1-21) or ER-/HER2- (26% predicted sensitive, DRFS 83%, CI 68-100; ARR 26%, CI 4-48) (Fig 1).[9] Predicted treatment sensitivity was significantly associated with lower relapse risk (HR 0.19, CI0.07-0.55) in a multivariate model including ER status, tumor and nodal stage, grade, age, and type of taxane treatment (paclitaxel or docetaxel).

As important as predicting chemosensitivity may be, outcomes for TNBC patients will not be improved unless targeted therapy is developed for patients with chemo-resistant disease. Recent advances in molecular profiling have identified subsets of TNBC (Fig. 2) with distinct molecular features targetable with existing FDA approved drugs.[1,7,10,11] Basal-like TNBCs (BL1 and BL2) are heavily enriched in cell cycle and cell division pathways. Gene expression profiling has revealed that these tumors have high expression of proliferation genes such as aurora kinases, *MYC*, *NRAS* and *PLK1* as well as elevated DNA damage response (BL1 subtype). These tumors may have higher rates of pCR to standard chemotherapy compared to other TNBC subtypes. The BL2 subset displays gene ontologies involving growth factor signaling such as EGFR and IGF1R pathways. Cell lines classified as basal-like had high rates of sensitivity to cisplatin and relative resistance to PI3K directed therapy in both cell culture and xenograft models. Though most triple-negative breast cancers are classified as basal-like (BL1 and BL2) by microarray analysis, approximately 30% of triple negative tumors are molecularly distinct from basal-like breast cancers as they display mesenchymal features, including enrichment in epithelial-to-mesenchymal transition (EMT) and stem-cell like characteristics. Subgroups with these features have been identified by independent investigators and have been termed mesenchymal (M), mesenchymal-stem cell like (MSL) and claudin-low. Mesenchymal-like TNBCs carry a high rate of molecular aberrations that activate the PI3K/Akt/mTOR axis suggesting that this subgroup may be responsive to therapeutic regimens targeting this pathway. Approximately 10-15% of TNBC are associated with expression of androgen receptor (AR+ or LAR) and approximately 20-25% are immune modulatory (IM), expressing genes associated with immune activation. Approximately 10-20% of patients with TNBC are carriers of germline BRCA1/2 mutations. When treated with NACT, pCR rates similar to slightly higher than non - carriers.[12] BRCA1 and BRCA2 are required for homologous recombination repair of DNA strand breaks leading to a defect in DNA repair in cancers harboring such mutations. As such, these tumors may be more sensitive to chemotherapy inducing DNA breaks or poly ADP-ribose polymerase (PARP) inhibitors.

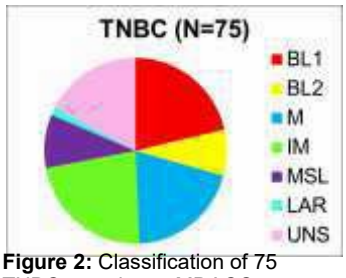
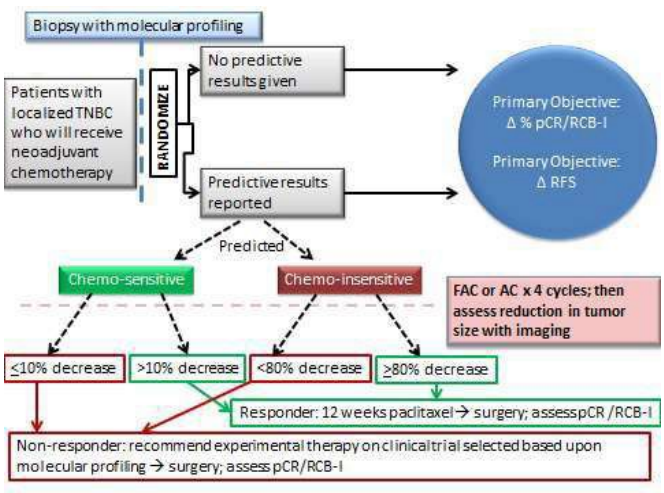


Figure 2: Classification of 75 TNBC samples at MDACC using signatures published by Pietenpol et al.[7]

Notably, investigators at MDACC also determined that rates of pCR/RCB-I to standard NACT were not statistically different amongst the subtypes, though the lowest rates of pCR were seen in the BL-2 subtype and the highest rates of RCB-III disease was within the mesenchymal subtypes, further validating the need for both predictors of chemotherapy sensitivity as well as molecular characterization of predicted chemotherapy-insensitive disease to determine appropriate therapy for patients with localizedTNBC.[12]

Given the disparity of treatment outcomes from NACT for TNBC, a molecular triaging protocol (MDACC 2014-0185) has been developed and IRB approved as a diagnostic platform to identify patients whose tumors are likely or unlikely to achieve pCR or RCB-I, in order to direct predicted responders toward standard chemotherapy and to direct predicted chemotherapy insensitive patients toward potentially more effective experimental therapies within clinical trials (Figure 3). Previously untreated patients with localized TNBC who are candidates for standard NACT (anthracycline =>taxane based therapy) will be enrolled into 2014-0185, a non-therapeutic, randomized trial where they will undergo biopsy of the primary tumor for molecular characterization within



the MDACC CLIA certified

Fig. 3 Clinical Trial Schema for 2014-0185

diagnostic lab, including predicted sensitivity to chemotherapy using gene signatures described above. Patients will be randomized 2:1 to know the results of the molecular characterization (given within 4-6 weeks after biopsy) or not know the results (treating physician blinded as well). *All patients will be treated the same except for this randomization (Figure 3).*

All patients will then initiate a planned 4 cycles of standard neoadjuvant anthracycline based chemotherapy based upon physician's choice (AC, dose-dense AC, FAC, EC or FEC are all allowed) with assessment of response by diagnostic imaging after 4 cycles of therapy (or at the time of progression in patients who develop clinical evidence of disease progression on chemotherapy). In our retrospective analysis of molecularly characterized patients with available diagnostic imaging, approximately 10-15% of patients will have obvious, extreme discordance between volumetric measurement of tumor response by ultrasound after 4 cycles of NACT and response prediction by gene signature with the diagnostic imaging best predicting outcome in these extreme cases of response or lack thereof (parameters outlined in Fig. 3). As such, patients with discordant imaging/molecular predictor results will be advised of these results and counseled to proceed based upon imaging. After response assessment, all patients will be offered the option of continuing forward with standard taxane (paclitaxel or docetaxel) or participation in clinical trials (Figure 4). Molecular characterization of the tumor (if known) can also be used by the treating physician to select for clinical trials within the BMO neoadjuvant clinical trials portfolio (Figure 4).

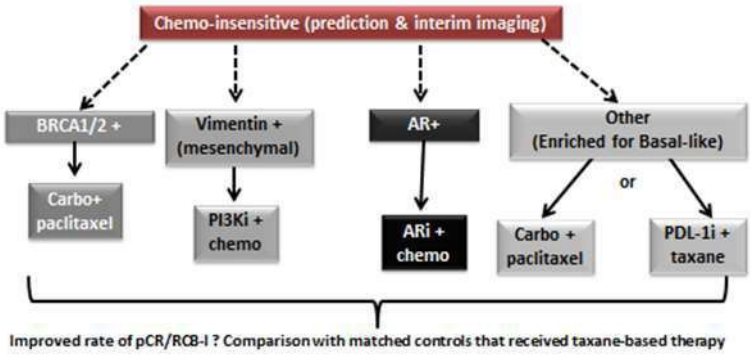


Figure 4: BMO Neoadjuvant Portfolio for Treatment of Chemotherapy Insensitive TNBC

Additionally, because of the 2:1 randomization in 2014-0185 (Figure 3), a subgroup of patients molecularly profiled will not know the results for decision -making (control arm). Like the experimental arm, patients on the control arm will be allowed to choose between study participation or to receive standard chemotherapy with paclitaxel based regimen for 12 additional weeks. Essentially, those who do not know the results of the molecular profiling are offered the same options as those who do, they simply will not have the molecular analysis to guide their decision making. Since all patients enrolled in 2014-0185 have biopsies for molecular characterization and diagnostic imaging, for research purposes all patients can be characterized as chemosensitive or chemoresistant and further subtyped into the TNBC molecular subtypes mentioned above. As such, those patients characterized with chemoresistant, subtype specific disease that receive standard NACT with taxane-based regimens can be compared with matched patients treated on clinical trials with targeted agents, such as PaCT. Though this comparison will not be a randomized comparison, it will provide evidence as to whether patients treated on a single arm phase II trial of targeted therapy derive additional clinical benefit and the comparison can be used to provide more robust data for confirmatory phase III clinical trial design. While our hypothesis is PaCT would be the best regimen for basal like TNBC. Likewise, patients whose tumors do not have mesenchymal features can be enrolled on this protocol and receive PaCT, which will allow a control group of non-basal TNBCs to serve as a control to determine the predictive value of potential biomarkers to define the mesenchymal population.

In summary, it is generally accepted that different subtypes of TNBC can be identified through modern molecular profiling techniques and that these subtypes contain potentially targetable molecular aberrations that would mandate different therapeutic approaches for each of the distinct subtypes. It is also generally accepted that the added toxicity associated with multi-drug therapeutic approaches necessitates exclusion of patients who are unlikely to benefit from an

investigational regimen. An unfortunate reality is that the modern molecular profiling techniques that have advanced our understanding of TNBC are not ready for use in patient selection to enrich for response in TNBC-subtype focused clinical trials, especially trials using archived paraffin embedded tissue as the source for analysis. As such, we are proposing an alternative strategy using an existing CLIA-compliant diagnostic test to identify patients with tumors that have basal like features (i.e. tumors with detectable EGFR staining). We are hopeful that this may help to further characterize which tumors are more likely to demonstrate response to the regimen.

2.2 Rationale for Panitumumab therapy in TNBC:

Epidermal growth factor receptor (EGFR) is overexpressed in all subtypes of breast cancer, with higher expression in TNBC.[14-16] Suppression of EGFR signaling in breast cancer has shown efficacy in controlling cancers by three main mechanisms. First, in our own pre-clinical work as well as other researchers reported that the EGFR suppression in breast cancer induced suppression of stem cell population [17-19] Secondly, suppression of EGFR pathway induces enhanced apoptosis in cancer cells via downstream MAPK/PI3K pathways. [20,21] Lastly, our preclinical study suggested that suppression of EGFR reduced the epithelial-mesenchymal transition (EMT) markers in breast cancer cells which are known to increase the metastatic potential of breast cancer cells.[22] Given the high rate of overexpression in TNBC, and the preclinical results on downstream effects of EGFR pathway suppression, we believe the suppression of EGFR in EGFR overexpression TNBC would have potential therapeutic potential. In recent study, when EGFR inhibiting small molecules were combined with genotoxic agents, the chemosensitivity of cells was enhanced. These researchers also reported that time-staggered EGFR inhibition, but not simultaneous co-administration, dramatically sensitizes a subset of triple-negative breast cancer cells to genotoxic drugs, such as doxorubicin and erlotinib respectively.[23] EGFR tyrosine kinase inhibitor such as erlotinib does have an anti-tumor activity against human inflammatory breast cancer cells, suggesting further benefit towards TNBC that harbors immunomodulatory pathway aberrations [Ueno's lab]. Mueller KL et al showed that gefitinib, EGFR-TKi, suppressed the growth of TNBC SUM149 cells[24]. Taken together, EGFR targeted therapy might have a promising role in TNBC.

Panitumumab is previously known as ABX-EGF. It is a fully humanized IgG2 monoclonal antibody with high affinity (Kd=5 x 10^{-11} M) that directly binds to the human EGFR. Panitumumab blocks the ligands EGF and TGFα binding to EGFR, inhibits the tumor growth, and elicits both tumor regression and eradication of established tumors in murine xenograft tumor models. The antineoplastic effects of Panitumumab in vivo have been demonstrated using human xenograft mouse models including breast cancers. Panitumumab has been shown to inhibit the growth of human epidermoid carcinoma A431 xenograft in athymic mice resulting in the complete regression of large (up to 1.2cm^3) established A431 tumors, regardless of initial tumor size. Lower doses of panitumumab administered twice weekly for 3 weeks inhibited growth of pre-existing solid tumors. Furthermore, a single injection of panitumumab (1mg) resulted in significant and prolonged tumor inhibition. Panitumumab in combination with FEC100 (5 -fluorouracil, epirubicin, and cyclophosphamide; 500/100/500mg/m^2) followed by docetaxel demonstrated with efficacious, acceptable toxicity as operable triple negative breast cancer in neoadjuvant setting.[25] They determined that pCR rates were 46.8% [95% confidence interval (CI): 32.5% to 61.1%] and 55.3% [95% CI: 41.1% to 69.5%]. The complete clinical response rate was 37.5%. They also reported toxicity, neutropenia grade 4 and febrile neutropenia, in 20.5% and 3.6% of cycles. Non - hematological toxicities were grade 3 and 4 acneiform rashes (35% and 8.3%), grade 3 dry skin (10%), and erythema (5%). No toxic deaths were reported.
Furthermore, the results of a clinical trial using panitumumab with weekly paclitaxel and carboplatin were reported32. Cowherd et al. conducted a single-arm phase II trial which enrolled metastatic or locally advanced TNBC using a treatment schedule of paclitaxel 80 mg/m2 and carboplatin AUC of 2 on days 1, 8, and 15 and panitumumab 6 mg/kg on days 1 and 15 for a cycle length of 28 days. The main result of this study was an overall response rate of 46%. The median time to best response was 2.4 months and median time to disease progression was 3.6 months.

Cowherd et al. concluded that the response rate and toxicity of panitumumab with carboplatin and paclitaxel was consistent with other reports using platinum based chemotherapy with targeted agents in metastatic TNBC.
Simultaneously, in a review of EGFR targeted treatments for breast cancer by Lluch et al. reported that existing EGFR treatment has limited benefits for breast cancer patients including TNBC33. The response rate of combination of the monoclonal antibody cetuximab with a platinum agent is a 15-20%. While the EGFR antibody gefitinib has some promising results in the ER positive population. It has not been identified as a predictive marker for the appropriate selection of the patients. Based on this information the selection of patients who may benefit from EGFR treatment needs to be refined with the help of biomarkers.

We are performing a single arm phase II study in patients with primary IBC without HER2 over-expression treated with panitumumab, Nab-paclitaxel, and carboplatin and FEC preoperative systemic chemotherapy (NCT01036087, institutional protocol #2008-0372). The median follow up time is 11.7 months (range; 8.7-33.9 months). This prospective study consists of 25 newly diagnosed IBC patients, 15 patients are ER/PgR+ and HER2- and 10 are TNBC. Nine patients achieved pCR; the response rate was 36% (95%CI; 0.18-0.58). Among 60% of TNBC, 20% of ER/PgR+ and HER2 - patients achieved pCR. The frequency of grade 3 or 4 hematological events were 18 (72%), grade 3 non-hematological toxic events were 5 (32%) and grade 4 was 0 during the panitumumab regimen (Data not published but submitted to ASCO). Higher proportion of TNBC patients who achieved pCR in this poor prognosis group of breast cancer patients further promoted the pursuit of EGFR inhibition in TNBC patients. We speculate such higher response in TNBC is due to higher expression of EGFR at baseline. Therefore, we hypothesize that EGFR overexpressing triple negative breast cancer will have a significant benefit from EGFR targeted therapy.

2.3 Rationale for Correlative Studies

EGFR suppression in breast cancer can induce several downstream changes. In addition to a routine - umbrella protocol based - molecular profiling of cancers, we propose to study such pathways that previously showed regulation by EGFR suppression. Suggested pathways are mainly 3, including stem cell population, EMT regulation, and apoptosis in addition to the confirmation of EGFR protein expression. To obtain more definitive biomarker changes induced by Panitumumab, we planned a one-week ”window” period of Panitumumab single agent treatment followed by a biopsy prior to the start of the combination PaCT regimen.

Immunohistochemistry (IHC): In lung cancer, where EGFR inhibitors are routinely used as predictive therapeutic biomarker, IHC for EGFR protein expression is the current standard of care. Patients who are enrolled in our study will have a baseline biopsy and an additional biopsy prior to initiation of the combination treatment that will be analyzed for EGFR gene expression/amplification. However, to confirm the convenient testing of EGFR using IHC technique, and consistency between gene amplification and protein expression in TNBC, we will also perform protein expression study using IHC for each sample. Additional IHC biomarkers that may be associated with response to neoadjuvant therapy including immune, cell cycle and oncogenic proteins such as PD-L1, Ki67, androgen receptor, PTEN, vimentin may be evaluated for correlative studies.

Stem cell population: We will analyze the baseline molecular profile of tumors as well as targeted stem cell population on patients who received PaCT regimen using stem cell markers. Proposed stem cell markers include CD24, CD44, and ALDH. When the quantity of the sample is limited, we will use previously validated stem cell detection technique CD44 variant antibody IHC staining to evaluate the proportion of stem cell within tumor sample.

EMT markers: As a panel to evaluate the EMT markers, in addition to routine gene expression analysis, we will separately perform IHC staining using CLIA certified antibodies for E Cadherin, Vimentin, as well as experimental antibodies of Nodal, Axl to evaluate the

changes in EMT markers, in pre-and post-treatment samples in comparison.

Apoptosis markers: To determine apoptosis activity induced by EGFR inhibition, cleaved caspase-8, caspase-3 will be stained by IHC technique, in pre-and post-treatment samples in comparison.

PD-L1 glycosylation: Recent study by collaborator Dr. Hung showed EGF/EGFR induces the glycosylation of PD-L1, and suppression of PD-L1 either by sugar analogue or EGFR inhibitor enhances the efficacy of anti-PD-1 therapy.

Blood Based Marker: In addition to tumor based analysis, peripheral blood can be collected to measure genomic changes. Serial monitoring of pharmacodynamics marker changes can reveal novel marker changes that cannot be detected by tumor response on short-term drug exposure. The TGIRT-Seq method was used to analyze plasma of metastatic breast patients by testing all RNA classes (mRNA and lincRNA, plus small ncRNAs such as Y RNA, tRNA and miRNA) together in one RNA-seq assay. CTCs will be further analyzed for single cell based DNA mutation NGS. Initial studies of plasma and tissues from patients with breast cancer have been promising in illustrating the ability of this method to obtain clinically relevant information about transcript patterns than cannot be obtained by conventional methods using plasma. Novel proteomic assays such as O-link, where we detect protein of interest by double-antibody detection sandwich technique, thereby increase the sensitivity of protein detection to overcome the current limitation of many proteomic techniques and Collaborative Enzyme Enhanced Reactive (CEER) assay, that enhances the detection of both intact and phosphorylated form of protein molecules therefore allowing detection of network-wide changes of small protein and phosphorylation changes that is induced by a drug, will be tested for proteomic landscape changes induced by the proposed treatment. These proteomic technologies are ultra-sensitive and highly specific protein measure assessment that can measure specific protein in the blood samples, while the exact sensitivity may need further validation.

Objectives

3.1 Primary Objective:

- To evaluate the pCR, RCB-0 and RCB-1 rates of patients with localized TNBC who were treated with PaCT in the neoadjuvant setting.

3.2 Secondary Objectives:

- To estimate progression free survival (PFS) distribution of localized TNBC patients who were non-responders to initial anthracycline and cyclophosphamide chemotherapy, and who were treated with the PaCT regimen in the neoadjuvant setting.
- Determine changes of EGFR downstream biomarkers one week after 1 dose of Panitumumab.
- Determine response rate after 4 cycles of PaCT using radiographic imaging.
- Correlate pathologic response with EGFR expression as measured by IHC.
- Determine toxicity associated to 4 cycles of PaCT in the neoadjuvant setting.
- Compare pathologic response to 4 cycles of PaCT in EGFR overexpressing tumors vs. non- EGFR overexpressing tumors.
- Compare pathologic response in tumors to 4 cycles of PaCT vs. 12 weeks of weekly paclitaxel (using data collected in conjunction with protocol 2014-0185).
- Determine pCR (RCB-0) alone as the response rate.

3.3 Exploratory Objectives:

- Determine the correlation between EGFR expression by IHC and the presence of enhanced EGFR gene signatures at the time of initial tumor biopsy prior to NACT (using gene expression data obtained from the protocol 2014-0185).
- Determine rates of pCR in patients with EGFR overexpressed tumors identified by gene signatures (using gene expression data obtained from protocol 2014-0185) and compare to pCR rates in non-EGFR overexpressed tumors.
- Determine the correlation between EGFR expression by IHC and the changes of EGFR downstream changes induced in surgery sample after completion of PaCT regimen.
- Determine the change in PD-L1 glycosylation induced by Panitumumab, and correlation with efficacy.
- Determine the change after treatment in blood-based markers, if any, and use these to predict a response to Panitumumab treatment.

4.0 Selection of Patients

4.1 Inclusion Criteria:

1) Patients must have an intact evaluable primary tumor, or biopsy proven axillary node involvement with at least 1.0 cm smallest dimension based on imaging after neoadjuvant anthracycline-based chemotherapy and prior to initiation of neoadjuvant chemotherapy under this protocol. Baseline measurements and evaluations must be obtained within 4 weeks of registration to the study. All areas of disease should be recorded in order to assess response and uniformity of response to therapy.
2) Triple-negative breast cancer defined as ER<10%; PR<10% by immunohistochemistry (IHC) and HER2 0-1+ by IHC or 2+, FISH < 2, gene copy number < 4.
3) Age ≥ 18 years.
4) Patients must have an ECOG performance status of 0 or 1.
5) Patients must have received at least one dose of an anthracycline based neoadjuvant regimen. Patients are eligible if therapy was discontinued due to disease progression or therapy intolerance.
6) Baseline MUGA or echocardiogram showing LVEF >/= 50% within 12 weeks prior to initiation of neoadjuvant chemotherapy.
7) Adequate organ function defined by the following parameters
    - Serum creatinine </= 1.5 mg/dl. Creatinine clearance (CrCl) >/= 50 mL/min calculated by the Cockroft-Gault method as follows: male creatinine clearance = (140 – age in years) x (weight in kg) / (serum Cr x 72); Female CrCl = (140 – age in years) x (weight in kg) x 0.85 / (serum Cr x 72).
    - ANC>/= 1500/mm^3, platelets >/= 100,000/mm^3
    - Hemoglobin >/=9.0 g/dL
    - SGOT (AST) and SGPT (ALT)< 3.0 x upper limit of normal
    - Alkaline phosphatase (Alp) </= 2.5 x ULN
    - Total bilirubin </=1.5 x ULN
8) Signed informed consent.

4.2 Exclusion Criteria

1) Patient is unwilling or unable to sign and date the IRB approved informed consent.
2) Patients with less than 1.0 cm measurable residual disease after neoadjuvant anthracycline based chemotherapy.
3) Women that are pregnant or lactating.
4) Patients with a history of prior malignancy within 5 years of study entry with the exception of curatively treated non-melanomatous skin cancer or carcinoma in situ of the cervix or breast.
5) Patients with a history of stage IV or metastatic disease.
6) Any serious medical illness, other than that treated by this study, which would limit survival to less than 1 month or psychiatric illness which would limit informed consent.
7) Known positive test(s) for human immunodeficiency virus infection, hepatitis C virus, acute or

chronic active hepatitis B infection.

8) Patients with a peripheral neuropathy > grade 1.
9) Patients with a history of serious cardiac events defined as: New York Heart Association class 3 or 4 heart failure, or history of myocardial infarction, unstable angina or CVA within 6 months of protocol registration.
10) Patients with a history of PR prolongation or AV block.
11) Patients with a history of prior therapy with paclitaxel and/or carboplatin.
12) Patients who have received a cumulative dose of doxorubicin of greater than 360 mg/m^2 or epirubicin of greater than 640 mg/m^2.
13) Patients who concurrently use hormonal therapy and/or concurrent radiation therapy.
14) Patients who had prior radiation therapy of the primary breast carcinoma or axillary lymph nodes.
15) Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during the study and 8 weeks after. Highly effective contraception methods include combination of any two of the following:
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS);
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository;
    - Total abstinence or;
    - Male/female sterilization.

    Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.
16) Male patients whose sexual partner(s) are WOCBP who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment.
17) Negative serum or urine pregnancy test for women within 72 hours of receiving the first dose of the study medication for women of childbearing potential.

5.0 Registration Procedures

Patients must not start protocol treatment prior to registration.

The following information will be requested:

Protocol Number

Investigator Identification

Investigator's name

Patient Identification

Initials

Patient Demographics

Sex
Birth Date (mm/yyyy)
Race
Ethnicity

Eligibility Verification

Patients must meet all of the eligibility requirements listed in section 4.1

Additional Requirements:

All patients must be provided with a signed and dated copy of the informed consent document.

Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted. The reason for not starting protocol treatment should be documented on one of the baseline forms. Also the date and type of the first non -protocol treatment that the patient receives should be documented.

6.0 Treatment Plan

6.1 Treatment

Patients will receive a single dose of Panitumumab, as a single agent, one week prior to the start of the treatment protocol. After this seven day "window period" patients will undergo an optional biopsy and correlative blood testing (+/- 1 day), then initiate the full PaCT combination (see Study Calendar).

Patients will initiate therapy at the doses and schedules listed in table 1. Each cycle will be defined as 21 days of therapy. Patients will undergo a planned 4 cycles of therapy prior to surgical resection. Patients who are unable to receive 4 cycles of therapy due to toxicity will be recorded in the toxicity analysis, but will be replaced for the efficacy analysis. Patients who develop disease progression during therapy will be included in the efficacy analysis. For drug administration guidelines and dose reductions, see section 6.3.

All patients will undergo surgical resection of their primary tumor unless they are deemed not fit for surgery after 4 cycles of therapy. Patients may undergo either lymph node sampling or complete axillary dissection as considered standard of care by their surgeon.

Table 1. Dosage of panitumumab, carboplatin, paclitaxel

Agent	Premedication: *precautions	Dose	Route	Schedule
Panitumumab	Not required for routine infusions	2.5 mg/kg	If no reaction to the first dose of panitumumab, 30 minutes for subsequent doses	Once per week X12
Paclitaxel	10 mg IV Dexamethasone, 15min prior.	80 mg/m2	IV over 60 minutes after completion of Panitumumab, through separate IV line	Once per week X12
Carboplatin	8 mg IV Ondansetron, 15 min prior	4 AUC**	IV over 30 minutes after completion of paclitaxel through separate IV line	Once every 3 weeks X4
* Only for hypersensitivity, antiemetic should be given accordingly. ** Total Dose (mg) = (target AUC) x (GFR+25)				

6.2 Drug Information

For Paclitaxel/Carboplatin, please refer to package insert.

Panitumumab (Vectibix®)
See Pharmacy guide in Appendix II.

Do not administer panitumumab as an intravenous push or bolus.

Preparation

Prepare the solution for infusion, using aseptic technique, as follows:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Although panitumumab should be colorless, the solution may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates (which will be removed by filtration; see below). Do not shake. Do not administer panitumumab if discoloration is observed.

- Withdraw the necessary amount of panitumumab for a dose of 6 mg/kg.
- Dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Do not exceed a final concentration of 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.

6.3 Panitumumab Administration

- Administer using a low-protein-binding 0.2 µm or 0.22 µm in-line filter. Panitumumab must be administered via infusion pump.
    - Flush line before and after panitumumab administration with 0.9% sodium chloride injection, USP, to avoid mixing with other drug products or intravenous solutions. Do not mix panitumumab with, or administer as an infusion with, other medicinal products. Do not add other medications to solutions containing panitumumab.

    - Infuse doses of 1000 mg or lower over 60 minutes through a peripheral intravenous line or indwelling intravenous catheter. If the first infusion is tolerated, administer subsequent infusions over 30 to 60 minutes. Administer doses higher than 1000 mg over 90 minutes.

- Use the diluted infusion solution of panitumumab within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36° to 46°F). DO NOT FREEZE.
- Discard any unused portion remaining in the vial.

6.4 Toxicity and Dose modification

Panitumumab

Dermatologic and Soft Tissue Toxicity: In randomized trial of metastatic colorectal cancer (mCRC) patients, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 15% of patients with mCRC receiving panitumumab. The clinical manifestations included, but were not limited to, acneiform dermatitis, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures.

Monitor patients who develop dermatologic or soft tissue toxicities while receiving panitumumab for the development of inflammatory or infectious sequelae. Life-threatening and fatal infectious complications including necrotizing fasciitis, abscesses, and sepsis have been observed in patients treated with panitumumab. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with panitumumab. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis). Withhold or discontinue panitumumab for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications.

Dose modification of Panitumumab: If the toxicities are deemed to be related to Panitumumab, two steps of dose reductions are permitted. Figure 6 provides guideline for reducing. The starting dose is 2.5 mg/kg. The panitumumab dose will be calculated based on the subject actual body weight at baseline and will not be re-calculated unless the actual body weight changes at least 10%.

Electrolyte Depletion/Monitoring: Progressively decreasing serum magnesium levels leading to severe (grade 3-4) hypomagnesemia occurred in up to 7% of patients across clinical trials. Monitor patients for hypomagnesemia and hypocalcemia prior to initiating panitumumab treatment, periodically during panitumumab treatment, and for up to 8 weeks after the completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Repletion magnesium and other electrolytes as appropriate is highly recommended.

6.5.1. Dose Modifications Panitumumab

If the toxicities are associated with panitumumab, two levels of dose reductions are permitted (Table 2). The starting dose is 2.5 mg/kg. The panitumumab dose will be calculated based on the patient's actual body weight at baseline and will not be re-calculated unless the actual body weight changes at least 10%.

Table 2. Panitumumab de-escalation schedule

Dose level	Panitumumab dose (mg/kg)
Starting dose	2.5
Level -1	2.0
Level -2	1.5
	DC Panitumumab*
* If panitumumab is discontinued due to panitumumab-associated toxicities, patient may continue to receive paclitaxel and carboplatin.	

For patients who experience panitumumab-associated grade 3 and grade 4 toxic effects while in the study, one or more doses of panitumumab may need to be withheld, delayed, or reduced. If panitumumab is withheld, or delayed for up to two cycles, on resolution of toxicity, two attempts to reduce panitumumab doses will be allowed. If patients continue to experience panitumumab-associated grade 3 or 4 toxicities after panitumumab is withheld for more than 2 cycles or after second dose reduction, panitumumab will be discontinued (Figure 6).

a. Criteria for withholding a dose of panitumumab

1.1.1.a.1. Skin- or nail-related toxicities:

- Symptomatic skin- or nail-related toxicity requiring narcotics, systematic steroids, or felt to be intolerable by the subject.
- Skin or nail infection requiring IV antibiotic or IV antifungal treatment
- Need for surgical debridement
- Any skin- or nail-related serious event (Appendix. I)

1.1.1.a.2. Non-skin or nail-related toxicities, any grade 3 or 4 toxicity with the following exceptions:

- Panitumumab only be withheld for symptomatic hypomagnesemia and/or hypocalcemia that persist despite aggressive magnesium and/or calcium replacement.
- Panitumumab will only be withheld for grade 3 or 4 nausea, diarrhea, or vomiting that persists despite of maximum supportive care.
- Panitumumab will only be withheld for grade $\geqslant$ 3 anemia or grade 4 thrombocytopenia that cannot be managed by blood transfusions or cytokine therapy.

b. Criteria for re-treatment with panitumumab

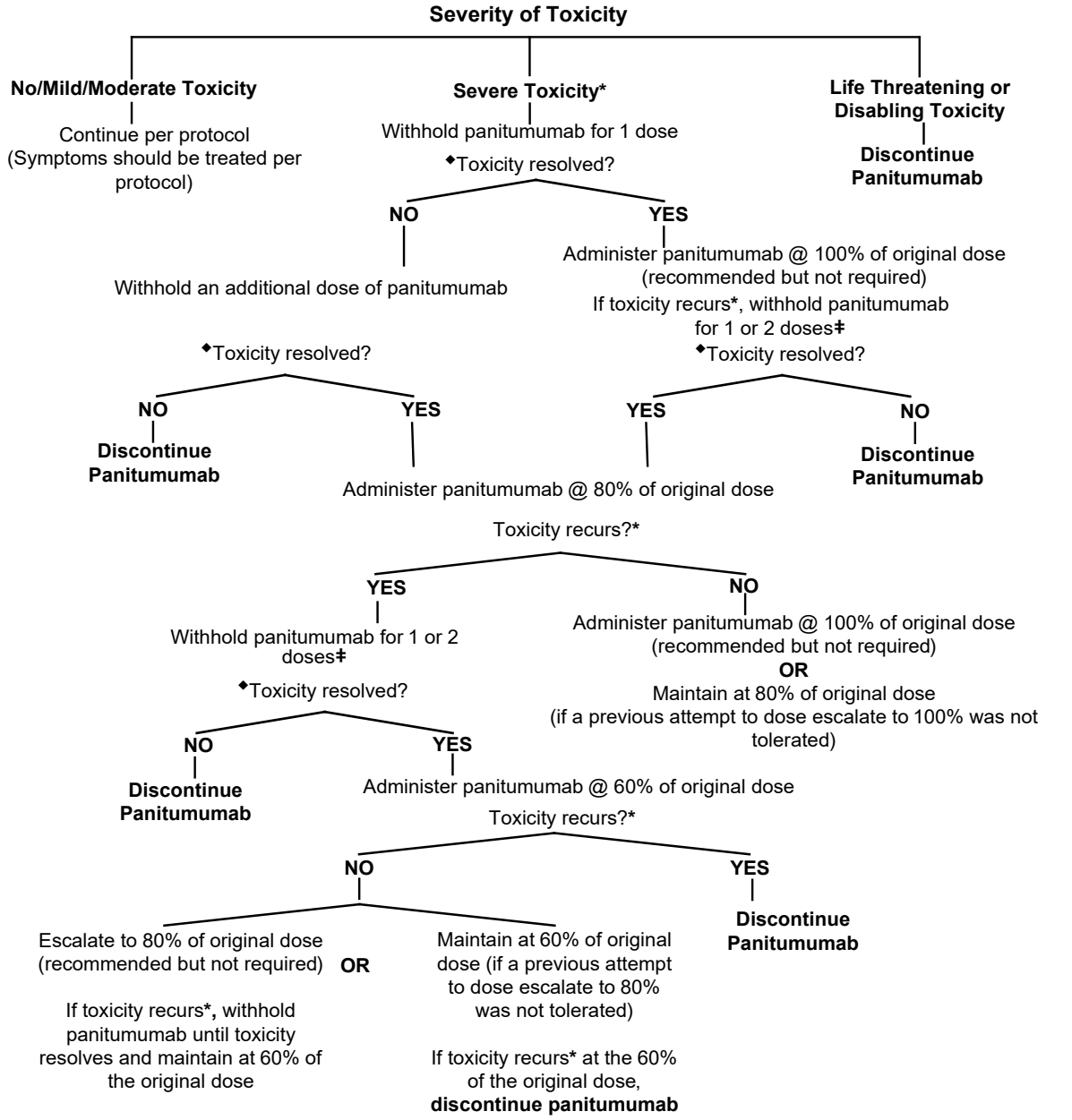
1.1.1.b.1. Skin-or nail-related toxicities: Panitumumab administration may recommence once:

- The adverse event has improved to $\leqslant$ grade 2 or returned to baseline; or the patient has recovered to the point to which symptomatic skin- or nail-related toxicity is considered tolerable; or systemic steroids are no longer required; or IV antibiotic or IV antifungal treatment is no longer required.

1.1.1.b.2. Non-skin- or nail-related toxicities:

- Panitumumab administration may recommence once the adverse event has improved to $\leqslant$ grade 1 or returned to baseline.

Fig 6. Algorithm of toxicity based dose modification of Panitumumab.



* Assess toxicity before each cycle. Toxicity recurs = meets the criteria for withholding a dose of panitumumab at any time during the study (See Section 4.1.6).

◆ Assess toxicity before each cycle. Toxicity resolved = meets the criteria for restarting panitumumab (see section 4.1.7). Subjects from whom > 2 subsequent cycles of panitumumab are required to be withheld should not be re-treated with panitumumab.

ą Up to 2 subsequent doses of panitumumab may be withheld but panitumumab may not be withheld longer than 6 weeks from the previous dose. The second dose should only be withheld if the toxicity has not resolved by the time that the subsequent cycle of chemotherapy is due.

6.5.2 Paclitaxel

- *Pre-medication:* If paclitaxel is being given then prior to commencing chemotherapy give paclitaxel hypersensitivity prophylaxis, including H1/H2 antagonists and corticosteroids, as per MD Anderson standards. Immediately prior to chemotherapy give anti-emetics as per local standards; this may include oral or intravenous 5HT3 antagonists.

- Paclitaxel should be given prior to carboplatin.

- *Caution*: Subjects who had a mild or moderate hypersensitivity reaction despite prophylactic medication have been successfully re-challenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended. Adequate clinical supervision, in accordance to institutional policy, must be present and appropriate intervention must be readily available to diagnose and treat hypersensitivity reactions. The following are recommendations for management of hypersensitivity reactions:

- Mild Symptoms: Complete study therapy. Supervise at bedside. No treatment required.

- Moderate Symptoms: Stop paclitaxel infusion. Consider oral or IV diphenhydramine and oral or IV dexamethasone. Resume paclitaxel infusion at the discretion of the treating physician following the recovery of symptoms. If paclitaxel is resumed, start at a low rate, (e.g., 20 ml/hour for 15 minutes) then increase as tolerated to a full dose rate until infusion is complete. If symptoms recur, stop paclitaxel infusion and do not re- challenge further with paclitaxel. Patient may continue on study at the discretion of treating MD with only Panitumumab and Carboplatin, but may not be re-challenged with paclitaxel.

- Severe, Life-Threatening Symptoms: Stop paclitaxel infusion. Give IV diphenhydramine and IV dexamethasone as above. Add epinephrine or bronchodilators if indicated. Patient may continue on study at the discretion of treating MD with only Panitumumab and Carboplatin, but may not be re- challenged with paclitaxel.

6.5.3 Carboplatin

Dosing: Use normally available stock in keeping with the standard local practice. There are no special drug accountability arrangements for carboplatin. Reconstitute carboplatin AUC 4 (calculated dose) or AUC4 (GFR measured), in 250ml of 5% dextrose according to local standard practice.
Allergic reactions to carboplatin are not a dose limiting toxicity and should be managed according to standard local practice. Patients may be re-challenged with increased prophylactic medications and/or slowing of infusion rates at the discretion of the treating physician. If it becomes necessary to discontinue carboplatin due to hypersensitivity then patients will continue treatment with paclitaxel and Trial Drug. The carboplatin dose should be calculated according to the Calvert formula as follows

- Carboplatin dose = Target AUC X (GFR + 25)

For the purpose of this protocol the GFR is considered equivalent to the creatinine clearance. The exact dose of carboplatin therefore depends on the GFR and the method of calculating the GFR will also affect the carboplatin dose. The GFR can be calculated using a variety of different formulae and should be calculated as per local practice.
If the estimated serum creatinine clearance is <50 ml/minute, then a formal measurement of the GFR is required, using either a 24 hour urine collection or an isotopic clearance. If the isotopic clearance is measured then the value uncorrected for body surface area (BSA) should be used in dose calculations.

The target AUC for carboplatin depends on the method of GFR assessment. Where the carboplatin dose is based on a GFR measured by isotopic clearance, or a 24hour creatinine clearance (urine collection), the target AUC is one unit **lower** than that based on the estimated GFR. This is summarized in Table 3.

Table 3: Target AUC Depending on GFR Calculation Method

Estimated GFR	**Measured GFR**
Cockcroft-Gault/Jellife/Wright	Isotopic/24hr Urine
AUC 4	AUC 4

Dose capping of carboplatin may be carried out according to standard MD Anderson practice.

Every effort will be made to administer the full-dose regimen. Dose adjustments are to be made according to the system showing the greatest degree of toxicity.

If the toxicities are deemed to be associated with paclitaxel or carboplatin, two levels of dose reductions are permitted. Table 4a provides guideline for reducing the dose of paclitaxel and carboplatin.

GFR Limitations for carboplatin dosing: Isotopic GFR is inaccurate in patients with significant effusions, ascites or edema as the isotope distributes into third space fluid collections.

Patients who have had complicated or prolonged post-operative recovery and who have been maintained on prolonged IV fluids with poor nutrition will have a falsely low serum creatinine.

Formulae, such as the Cockcroft-Gault formula, are inaccurate at the extremes of age and weight. The calculated GFR may be falsely high in obese young women and falsely low in thin, elderly women.

It is assumed that clinicians entering patients into this protocol will be aware of these issues and the clinical judgment of an experienced clinician should be applied to the calculation of the carboplatin dose.

Table 4a. Paclitaxel and carboplatin de-escalation schedule

Dose level	**Paclitaxel dose (mg/m^2)**	**Carboplatin dose (AUC)**
Starting dose	80	4
Level -1	60	Modified GFR to reduce the dose per physician's discretion
Level -2	Hold	Modified GFR to reduce the dose per physician's discretion
	Off study*	Off study*
* If paclitaxel and/or carboplatin continue to cause chemotherapy-related toxicities at dose level-2, patient will be removed from the study.		

Depending on the extent of toxicity, dose reduction may be needed for only one drug (paclitaxel or carboplatin) or for both drugs. If the investigator is unsure of which type of reduction is needed, both drugs should be reduced. If the toxicity level indicates that only one drug should be reduced, the other drug should be remain at its original dose level. If the potentially dangerous toxicities are observed, the investigator and sponsor should be discuss the options for dose reductions.
Doses that have been reduced as a results of toxicity must not be re-escalated back to the starting level.
Treatment may be delayed no more than 4 weeks to allow recovery from toxicities.
If the toxicities are associated with paclitaxel and carboplatin, a maximum of two dose reductions will be allowed per patient.

Patients who are age 65 years old or older will have the risk of carboplatin-associated toxicity calculated by the CARG score (Table 4c) (http://www.mycarg.org/Chemo_Toxicity_Calculator).[37] We highly recommended that patients who have an intermediate (6 to 9 points; 52%) or high (10 to 19 points; 83%) CARG risk score consider dose modification of carboplatin (see Table 4b).

Table 4b. Carboplatin de-escalation schedule for 65 years old or older

CARG score	Carboplatin (AUC)
Low risk (0 to 5 points)	4
Intermediate risk (6-9 points)	Modify per physician's discretion
High risk (10-19 points)	Modify per physician's discretion

Table 4c. CARG score[37](J Clin Oncol. 2011 Sep 1;29(25):3457-65, Table 5.) (http://www.mycarg.org/Chemo_Toxicity_Calculator)

Risk factor	Score
Age≥72	**2**
Cancer type GI or GU	**2**
Chemotherapy dosing, standard dose	**2**
No. of chemotherapy drugs, polychemotherapy	**2**
Hemoglobin<10g/dl (female)	**3**
Creatinine clearance (Jelliffe, ideal weight)<34 ml/min	**3**
Hearing, fair or worse	**2**
No. of falls in last 6 months, 1 or more	**3**
IADL: taking medications, with some help/unable	**1**
MOS: Walking 1 block, somewhat limited/limited a lot	**2**
MOS: Decreased social activity because of physical/emotional health, limited at least sometimes	**1**
Abbreviations: GU, genitourinary; IADL, instrumental activities of daily living; MOS, Medical Outcome Study	

NOTE: All toxicities should be graded according to the NCI Common Toxicity Criteria (version 4.0)

All dose modifications must be recorded in the data capture system.

7 Reporting of Adverse Events

7.1 Assessment of Safety

Safety assessments will consist of monitoring and reporting AEs and SAEs per protocol. This includes all events of death, and any study-specific issue of concern

7.2 Adverse Events

- An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol imposed intervention, regardless of attribution.
- This includes the following:
- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms that were not present prior to the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- All adverse events will be recorded in the patient's electronic medical record, electronic database, and/or the AE log. The PI or designee will be responsible for determining attributions for each AE. The PI will be responsible for the sign off of all AE logs.

7.3 Serious Adverse Events (SAE) Reporting

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

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

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

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

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas MD Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices".

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported in accordance with the timeframes and procedures outlined in "The University of Texas MD Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". This may include the development of a secondary malignancy.

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

  The principal investigator has the obligation to report all serious adverse events to the FDA and IRB.

7.3.1 The PI and the research team is responsible for compliance with expedited reporting requirements for serious and unexpected and related adverse events (SUSARs) to Amgen Global Safety at 1-888-814-8653.

Please see most recent version of the IB for a sample form for reporting of these events.

MDACC SAE form will be used for the reporting of these events.

Table 5.

Safety Data	Timeframe for Submission to Amgen
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Sent to Amgen at time of regulatory submission
Serious Adverse Events (SAEs)	Individual reports batched to Amgen every 90 days
Pregnancy/Lactation	Within 10 days of investigator awareness
All SAEs and AEs Fatal AEs AEs leading to panitumumab discontinuation Related SAEs and AEs	End-of-study summary tabulations

The PI will notify Amgen of protocol amendments and follow institutional procedures to obtain necessary IRB approvals.

8.0 Supportive Care

All supportive measures consistent with optimal patient care should be given throughout the study. Exceptions include the use of erythropoietin to treat therapy-induced anemia. Investigators who choose to use myeloid growth factors should administer either GCSF or pegylated GCSF beginning on either day 2 or 3 of each cycle. The use of growth factor support should follow ASCO guidelines.

9.1 Duration of Therapy

Patients will receive protocol therapyunless:

- Patient experiences unacceptable drug toxicity.
- Patient withdraws consent.
- Patient has progression of disease as defined in section 6.0.
- The patient completes the required 4 cycles of therapy.
- Pregnancy

10.0 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed until 1 month after surgical resection of the tumor. Date of last follow up clinic visit should be within 30 days (+/- 10 days) of surgical resection. Investigators will also collect data on recurrence for 2 years after surgical resection of the tumor. Should a patient withdraw consent,

then the patient will be removed from study at that time and no further data will be collected.

11.0 Protection of human subjects

All current FDA, NCI, state federal and institutional regulations concerning informed consent will be followed.

In order to protect confidential patient information, all study participants will be assigned a study ID number. Specimens will be assigned a separate specimen ID number. All study information will be stored on password-protected computer files. Only authorized study personnel will have access to these files.

12.1 Scheduled evaluations

12.2 Pretreatment Evaluation

- Medical history and physical examination including weight and performance status.
- Laboratory studies: CBC with differential, sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT], serum or urine pregnancy test (WOCBP).
- Radiologic evaluation of measurable disease within 4 weeks of starting treatment.
- Patient must sign IRB-approved informed consent prior to any study-specific procedures unless such procedures are part of the standard of care.

12.3 Evaluation During Study

- Physical examination (including vital signs, weight, performance status): on day 1 of (or up to 3 days prior to) each treatment cycle.
- CBC with differential, sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT] within 48 hours prior to starting each cycle of therapy.
- Patients will undergo repeat imaging (mammogram, ultrasound and/or MRI, as clinically indicated) of the involved breast and axillary nodal basin as standard of care prior to surgical resection (after 4 cycles of therapy) or at the time of clinically suspected disease progression.

13.1 Measurement of Effect

13.2 Pathologic response

The RCB is a continuous variable derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden. RCB can be divided into four classes (RCB-0 to RCB-III) and will be collected as part of the study.

RCB-0 (pCR), Minimal RCB (RCB-I), Moderate RCB (RCB-II), and Extensive RCB (RCB-III).

The following parameters are required from pathologic examination in order to calculate Residual Cancer Burden (RCB) after neoadjuvant treatment:

The largest two dimensions (mms) of the residual tumor bed in the breast (largest tumor bed if multicentric disease)

Submission of the entire largest cross-sectional area of the residual tumor bed for histologic mapping, with specific identification of those slides in the pathology report (e.g. "the largest cross-sectional area of primary tumor bed was submitted in cassettes A5 - A9")

If the residual tumor is large (i.e. largest diameter > 5 cm), then at least 5 representative cassettes from the largest cross-sectional area are sufficient, but should be identified in the original pathology report (e.g. "representative sections from the largest cross- sectional area of primary

tumor bed were submitted in cassettes A5 - A9")

Histologic assessment of the percentage of the tumor bed area that contains carcinoma (all carcinoma, i.e. invasive and in situ), select one of the following:

0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%
To assess cellularity it is helpful to scan across the sections of tumor bed and then estimate the average cellularity from the different microscopic fields.

When estimating percentage cancer cellularity in any microscopic field, compare the involved area with obvious standards, e.g. more or less than half, one quarter, one fifth, one tenth, one twentieth, etc.

Expect there to be variable cellularity within the cross section of any tumor bed, but estimate the overall cellularity from the average of the estimates in different microscopic fields of the tumor bed.

e.g. if cellularity in different fields of the tumor bed were estimated as 20%, 10%, 20%, 0%, 20%, 30%, then an average estimate of overall cellularity would be 20%.

Histologic estimate of the percentage of the carcinoma in the tumor bed that is in situ, select one of the following:

0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%

The number of positive (metastatic) lymph nodes

The largest diameter (mm) of the largest nodal metastasis

The RBC can be accessed online: www.mdanderson.org/breastcancer_RBC

13.3 Radiographic Imaging

- Radiographic criteria of response will be based on the on regional ultrasound examination (decrease in size of the primary tumor and/or fatty replacement in regional lymph nodes)
- A decrease in size of the product of the two largest dimensions should =/> 50% will be considered a partial response.
- Complete disappearance of the primary tumor by physical exam and or ultrasound and normalization of the lymph nodes by ultrasound will be considered a complete clinical response.
- Progression of disease will be defined as 30% increase in the size of the primary tumor and/or lymph nodes on physical exam and/or ultrasound.

14.0 Correlative Studies

All molecular correlative studies will involve molecular profiling data generated through biopsy of the primary breast tumor and profiled within the existing BMO molecular triaging protocol that is currently IRB approved (MDACC 2014-0185).For Patients who were previously not consented to protocol 2014-0185, we will attempt to retrieve archival tissue from the initial diagnostic biopsy if available, to conduct additional correlative studies. Potential biomarkers of response will be correlated with pathologic response to PaCT using appropriate statistical analyses for the biomarker of interest (see rationale section).

Peripheral Blood
These samples will be used to perform correlative studies aimed at identifying predictive markers and to enhance the understanding of EGFR inhibition in the neoadjuvant setting.

15.0 Statistical Considerations

Overview

This is a non-randomized open label phase II study. Counting pCR (RCB-0) or RCB-I as response, a two-stage Gehan-type design will be employed with 14 patients in the first stage. If at least one patient responds, 33 more patients will be added for a total of 47 patients. This design has a 49% chance of terminating after the first stage if the true response rate is 0 .05, 23% chance if the true rate is 0.10, 10% if the true rate is 0.15 and 4% if the true rate is 0.20. If accrual continues to the second stage and a total of 47 patients are enrolled, the 95% confidence interval for a 0.20 response rate will extend from 0.10 to 0.35.

The proportion of patients with pCR (RCB-0) or RCB-I as the response rate along with an appropriate 95% confidence interval will be estimated, as well as the proportion of patients in the remaining RCB categories with confidence intervals as well. We will estimate the PFS distribution using the Kaplan-Meier method from the date of enrollment onto this study until the date of progression or death without evidence of progression. Patients alive and disease-free at the latest clinical evaluation will be censored at the date of that evaluation. We will also estimate the OS distribution in a similar fashion.

16.0 Secondary Objectives and Correlative Studies:

Potential biomarkers of response will be correlated with pathologic response to this treatment using appropriate statistical analyses for the biomarker of interest.

A secondary objective of this study is to also estimate the PFS distribution. PFS is defined as the time from enrollment to progression of disease (> 20% increase in tumor size as defined in Section 10.1) or death whichever comes first.

We will estimate the proportion of patients with pCR (RCB-0) or RCB-I as the response rate along with an appropriate 95% confidence interval. We will estimate the proportion of patients in the remaining RCB categories with confidence intervals as well. We will estimate the PFS distribution using the Kaplan-Meier method from the date of enrollment onto this study until the date of progression or death without evidence of progression. Patients alive and disease-free at the latest clinical evaluation will be censored at the date of that evaluation.

Early drop outs (i.e., patients not getting to surgery) should be counted as treatment failures (i.e., non-responders with RCB > 1).

If no RCB-0 or -1 response has been observed prior to enrolling the 15th patient, enrollment will stop until all of the 14 patients in the first stage are evaluable and resume only if a response has been documented.

Comparison will be made to patients from the parent study (2014 -0185) who received taxane-based therapy using matched propensity score methods for toxicity, pathologic response (RCB) and PFS.

Recent findings by Yau et al. (2019) indicated that TNBC patients with RCB-I have a slightly worse event free survival than patients with PCR (26). Therefore as a secondary objective, we will determine pCR (RBC-0) alone as a response rate. Currently, 5 patients enrolled on this study have had a pCR. If these numbers hold and we end with 5/37 (13.5%) patients with pCR, then the exact 95% confidence interval around this number will be barely below 5%, which will be inconclusive. If we increase by 10 patients to a total of 47, then if we have 7/47 patients with a pCR, the exact 95% CI will have a lower bound of 6.2%, which will provide the conclusive evidence we need to move forward with the analysis.

17.0 Inclusion of Minorities

The study will be available to all eligible patients regardless of race, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race or ethnicity.

18.0 Study Calendar

The Study Calendar summarizes the study procedures to be performed at each visit. Due to scheduling, these visits can occur +/- 3 days from the required time point. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

STUDY WEEK		**Window Period**	**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**				**Post Treatment**
STUDY DAY	**-28 to 0**	**1 week**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**Surgical Resection**	**Follow Up**
Informed Consent	X															
Demographics	X															
Medical History	X															
General Physical [a]	X		X			X			X			X				X[f]
Vitals Signs, Weight [a]	X		X			X			X			X				
Performance Status [a]	X		X			X			X			X				
Baseline Symptoms /Toxicities	X		X			X			X			X				
CBC	X		X	X	X	X	X	X	X	X	X	X	X	X		
Chemistries Chem 12 and LFTs [b]	X		X			X			X			X				
Pregnancy Test (Serum or urine)	X															
Radiographic Evaluation [c]	X													X		
Correlative Studies [d]	X	X						X							X	
Panitumumab		X	X	X	X	X	X	X	X	X	X	X	X	X		
Carboplatin			X			X			X			X				
Paclitaxel			X	X	X	X	X	X	X	X	X	X	X	X		

a. Physical examination (including vital signs, weight, performance status): on day 1 of (or up to 3 days prior to) each treatment cycle

b. CBC with differential, sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT] within 48 hours prior to starting each cycle of therapy

c. Patients will undergo repeat imaging (mammogram, ultrasound and/or MRI, as clinically indicated) of the involved breast and axillary nodal basin as standard of care prior to surgical resection (after 4 cycles of therapy) or at the time of clinically suspected disease progression.

d. Correlative Study samples will be collected at: Baseline, 1 week (+/- 1 day) after the first dose of Panitumumab, mid-treatment and before surgery.

f. Patient tracking by the study team will take place per standard of care adjuvant measures for PFS analysis. This will be completed by way of a physical examination every 3-4 months.

19.1 References :

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Appendix I. Dermatology/Skin/Nail Assessment (from CTCAE version 4.0 with modifications)

AE (Short Name)	Grade 1	Grade 2	Grade 3	Grade 4
Nail changes (Nail changes)	Discoloration; ridging (koilonychias; pitting) paronychia: intervention not indicated	Partial or complete loss of nail(s); pain in nailbed(s), paronychia: intervention indicated	Interfering with activities of daily living (ADL)	___
Erythema (Erythema)	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated
Pruritis/itching (Pruritis)	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	___
Rash: acne/acneiform (Acne)	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; lifethreatening consequences
Rash maculo-papular	Macules/papules covering	Macules/papules covering 10 -	Macules/papules covering	___

	<10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	>30% BSA with or without associated symptoms; limiting self care ADL	
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss

***Desquamation is defined as sloughing of skin and does not apply to dry flaking skin.**

Appendix II. Panitumumab Pharmacy Guide

Packaging, Formulation, Labeling and Storage

Panitumumab will be manufactured and packaged by Amgen and distributed using Amgen's clinical trial drug distribution procedures. Each vial of panitumumab will contain 10 mL of a sterile protein solution containing a 20-mg/mL solution of panitumumab. The vial will contain approximately 200 mg of panitumumab and is for single dose use only. Each vial of panitumumab will be labeled in accordance with current ICH GCP, FDA and specific national requirements.

The supplied investigational drug must be stored at 2-8° C in a secured area upon receipt. As panitumumab contains no preservatives, vials are designed for single use only. Exposure of the material to excessive temperature above or below this range should be avoided. Do not allow panitumumab to freeze and do not use if contents freeze in transit or in storage. If vials fall out of specified temperature requirement, please contact Amgen for instructions.

Records of the actual storage condition during the period of the study must be maintained (ie, records of the date and time and initials of person checking, and the "working day" temperature of the refrigerator used for storage of trial supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording).

Preparation

NOTE: Panitumumab is a protein and should be handled gently to avoid foaming, which may lead to denaturation of the protein product. This precaution applies not only to panitumumab stored in the vial, but also for diluted panitumumab prepared in the IV bag. It is, therefore, essential to avoid medication delivery methods, particularly pneumatic tube systems that could potentially lead to excessive shaking or vibration that would lead to particulate formation in the protein product.

Panitumumab must be prepared as an intravenous infusion using aseptic techniques. The dose of panitumumab will be 6 mg/kg (or 9mg/kg, depending on the study) and will be based upon the subject's baseline weight. The dose of panitumumab is required to be recalculated only when the subject's body weight increases or decreases by $\geq$ 10% from the original screening/baseline weight. This weight will be considered the new baseline weight from which a $\pm$ 10% variance is allowed before another recalculation is necessary.

The calculated amount of panitumumab (may be rounded to the nearest ten milligrams [eg, 456 mg rounded to 460 mg or 312 mg rounded to 310 mg]) will be removed from the vials and added to a minimum volume of 100 mL of pyrogen-free 0.9% sodium chloride solution USP. The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL. In the event a subject's actual body weight requires greater than a 150-mL volume infusion, panitumumab will be administered over 60 to 90 ± 15 minutes, as tolerated. The panitumumab will be infused within 19 hours of dilution and will be labeled per site pharmacy standard operating procedures. The bag should be labeled per site pharmacy standard operating procedures and promptly forwarded to the clinic center for infusion.

Supply and Return

At study initiation and as needed thereafter, panitumumab will be shipped to a responsible person (eg, a pharmacist) at the Investigator's institution, who will check the amount and condition of the drug and enter these data into the Proof of Receipt Form and Investigational Product Accountability record. The Proof of Receipt Form should then be returned to Amgen Inc., and the original retained at the site. At the end of the study, or as directed, all panitumumab supplies, including unused, partially used, or empty containers, will be destroyed at the site.

Panitumumab Accountability

An Investigational Product Accountability Record for the panitumumab must be kept current and should contain:

- The dates and quantities of panitumumab received from Amgen Inc.
- Manufacturing batch or lot numbers for product received
- Subject's identification (subject number)
- Date and quantity of panitumumab dispensed (and remaining, if from individual subject drug units)
- The initials of the dispenser
- Dose preparation records
- Date and quantity of drug returned to the investigator/pharmacy, if appropriate

Any discrepancies must be documented and subsequently reported to Amgen Inc. immediately.

These inventories must be made available for inspection by authorized sponsor representative(s) and regulatory agency inspector(s). The investigator is responsible for the accountability of all used and unused trial supplies.