MONOCLONAL ANTIBODIES

ALEMTUZUMAB
(CAMPATH® 1H)

I. MECHANISM OF ACTION

Antibody-dependent lysis of leukemic cells following cell surface binding. Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody that is directed against surface glycoprotein CD52. CD52 is expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, a subpopulation of granulocytes, and tissues of the male reproductive system (CD 52 is not expressed on erythrocytes or hematopoietic stem cells). The alemtuzumab antibody is an IgG1 kappa with human variable framework and constant regions, and complementarity-determining regions from a murine monoclonal antibody (campath 1G).

II. PHARMACOKINETICS

C_{max} and AUC show dose proportionality over increasing dose ranges. The overall average half-life is 12 days. Peak and trough levels of Campath rise during the first weeks of Campath therapy, and approach steady state by week 6. The rise in serum Campath concentration corresponds with the reduction in malignant lymphocytes.

III. DOSAGE AND ADMINISTRATION

Campath can be administered intravenously or subcutaneously.

Intravenous: Alemtuzumab therapy should be initiated at a dose of 3 mg administered as a 2-hour IV infusion daily. When the 3 mg dose is tolerated (i.e., ≤ Grade 2 infusion related side effects), the daily dose should be escalated to 10mg and continued until tolerated (i.e., ≤ Grade 2 infusion related side effects). When the 10 mg dose is tolerated, the maintenance dose of 30 mg may be initiated. The maintenance dose of alemtuzumab is 30 mg/day administered three times a week on alternate days (i.e. Monday, Wednesday, and Friday), for up to 12 weeks. NOTE: single doses of alemtuzumab > 30 mg or cumulative weekly doses of > 90 mg should not be administered since higher doses are associated with an increased incidence of pancytopenia. All doses should be administered as a 2 hour infusion, and should not be administered as an IV bolus.

Subcutaneous: On Day 1, 3mg of alemtuzumab administered SQ. If tolerated then 10 mg SQ was given on Day 3, and then increase to the target of 30 mg/dose from Day 5 onwards. The 30 mg dose is administered 3 times per week. Some centers administer SQ Campath witout titration of the dose initially.

NOTE: If the patient has a break in treatment of greater than 7 days, the initial slow titration up to the maintenance dose should be reinitiated.

DOSE MODIFICATION FOR HEMATOLOGIC TOXICITY

Hematologic Toxicity	Dose modification and Re-initiation of Therapy
For 1st occurrence of ANC ≤ 0.25 x 10^9/L and/or platelet count ≤ 25 x10^9/L.	Withhold Campath therapy. When ANC ≥ 0.5 x 10^9/L and platelet count ≥ 50 x10^9/L, resume Campath therapy at the same dose. If delay between dosing is ≥ 7 days, initiate therapy at 3 mg and escalate to 10 mg and then to 30 mg as tolerated.
For 2nd occurrence of ANC < 0.25 x 10^9/L and/or platelet count ≤ 25 x10^9/L.	Withhold Campath therapy. When ANC ≥ 0.5 x 10^9/L and platelet count ≥ 50 x10^9/L, resume therapy at 10mg. If a delay between dosing is ≥ 7 days, initiate therapy at 3mg and escalate to 10 mg daily.
For 3rd occurrence of ANC < 0.25 x 10^9/L and/or platelet count ≤ 25 x10^9/L.	Discontinue Campath therapy permanently.
For a decrease of ANC and/or platelet count to ≤ 50% baseline value in patients initiating therapy with a baseline ANC ≤ 0.5 x 10^9/L and/or a baseline platelet count ≤ 25 x10^9/L.	Withhold Campath therapy. When ANC and/or platelet count return to baseline values, resume therapy. If the delay between dosing ≥ 7 days, initiate therapy at 3 mg and escalate to 10 mg and then to 30 mg as tolerated.

IV. TOXICITY

A) Infusion-related events: Hypotensions, rigors, fever, shortness of breath, bronchospasm, chills and/or rash have been commonly reported with administration of alemtuzumab. Premedication with acetaminophen and diphenhydramine prior to infusion significantly reduced the likelihood of such reactions. Therapy with alemtuzumabis typically titrated upwards from a low dose in an attempt to minimize these side effects.

B) Hematologic: Anemia, neutropenia and thromycobytopenia occur commonly with Campath therapy. In early clinical trials Grade 3/ 4 neutropenia was seen in 70% patients; Grade 3/ 4 thrombocytopenia was seen in 52% cases; Grade 3/ 4 lymphopenia was seen regularly; and Grade 3/ 4 anemia in 47% patients.

C) Infections - serious, sometimes fatal bacterial, viral, fungal and protozoan infections have been reported in recipients of alemtuzumab. Prophylaxis against PCP and herpes virus infections is recommended and may decrease, but not eliminate the occurrence of these infections. CMV reactivation must be considered.

V. CLINICAL MONITORING:

Complete blood counts (including platelets) should be obtained at weekly intervals during Campath therapy and more frequently if worsening anemia, neutropenia, and/or thrombocytopenia is observed on therapy, and traditionally resolved within 4 weeks. CD 4+ counts should be assessed after treatment until recovery to ≥ 200 cells/microL. Weekly CMV reactivation monitoring is also required.

BEVACIZUMAB
(AVASTIN®)

I. MECHANISM OF ACTION

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biological activity of human vascular endothelial growth factor (VEGF). Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors led to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in mice caused reduction of microvascular growth and inhibition of metastatic disease progression [Reference: http://www.fda.gov/cder/foi/label/2006/125085s085lbl.pdf].

II. PHARMACOKINETICS

A) Bevacizumab clearance varies by gender, body weight, and tumor burden. After correcting for body weight, males have a higher bevacizumab clearance than females. Patients with higher tumor burdens (at or above median value of tumor surface area) have a higher bevacizumab clearance.
B) The half-life of bevacizumab is 20 days (range 11 – 50 days), and C_{ss} is reached in 100 days.
C) No adjustments in dose need to occur for age or sex.
D) Dose modification in hepatic dysfunction: no studies have been performed in this setting, so no dose modifications are available.
E) Dose modification in renal dysfunction: no studies have been performed in this setting, so no recommendations are available.

III. DOSAGE AND ADMINISTRATION

A) Available as a 100 mg/4 mL vial and 400 mg/16 mL vial.
B) Recommended dose of bevacizumab is 5 mg/kg once every 14 days as an IV infusion administered over 90 minutes. If the first infusion is well tolerated the second infusion may be administered over 60 minutes. If the second infusion is well tolerated the 3rd and all subsequent infusions can be administered over 30 minutes.
C) Dilute in 100 mL NS.
D) Do not administer or mix with dextrose solutions.
E) Do not administer as iv push or bolus.
F) Bevacizumab should be permanently discontinued in patients who develop GI perforation. Temporarily suspend treatment in patients who develop moderate to severe proteinuria (risk of continuation not known).

IV. TOXICITY

A) Hemorrhage: Two patterns of hemorrhage reported with use of bevacizumab. Minor hemorrhage classified as grade 1 epistaxis. Major hemorrhage classified as serious and reported fatalities have occurred in patients with non-small cell lung cancer. Patients with recent hemoptysis should not receive bevacizumab. This is a black box warning.
B) Congestive Heart Failure: Grade 2-4 reported in 2% of patients receiving bevacizumab. In patients receiving concurrent anthracyclines and bevacizumab the incidence of Grade 2 – 4 CHF increased to 14%. In patients that have received prior anthracycline therapy and/or left chest wall irradiation, the incidence of Grade 2-4 CHF is 4%.

C) Gastrointestinal Perforations/Wound Healing (Black Box Warning). The incidence of GI perforation with bolus bevacizumab was 2%. Typical presentation was abdominal pain associated with constipation and nausea. Include GI perforation in a differential diagnosis of patients presenting with abdominal pain. Permanently discontinue bevacizumab in patients with abdominal perforation or wound dehiscence requiring medical intervention.

D) Hypertension/Hypertensive Crisis

Blood Pressure	IFL + PL	IFL + BEVACIZUMAB	5-FU/LV + PL
>150/100mmHg	43%	60%	67%
Severe >200/110	2%	7%	10%

Permanently discontinue bevacizumab in patients with hypertensive crisis or hypertensive encephalopathy. Temporarily suspend therapy in patients with severe hypertension not controlled with medical management.

E) Proteinuria: The incidence of proteinuria is greater in recipients of bevacizumab than in those receiving chemotherapy alone.

F) Nephrotic Syndrome occurred in 0.5% patients in clinical trials. Discontinue bevacizumab therapy in patients who develop nephrotic syndrome.

G) Infusion related adverse events (IRAE): < 3% infusions were interrupted as a consequence of severe IRAE's.

H) Wound healing complications: bevacizumab administration can result in the development of wound dehiscence, in some cases resulting in fatality. Bevacizumab should be immediately discontinued in patients with wound dehiscence requiring medical intervention. The appropriate interval between termination of bevacizumab and subsequent elective surgery required to avoid the risks of impaired wound healing/dehiscence has not been determined.

I) Arterial thrombotic events: occur at a higher incidence in patients receiving bevacizumab than those receiving chemotherapy alone. In a pooled analysis of clinical trials involving 1745 patients the arterial thrombosis rate was 4.4% in the bevacizumab recipients and 1.9% in the chemotherapy alone recipients.

J) Reversible posterior leukoencephalopathy syndrome (RPLS): RPLS has been reported in clinical studies (incidence < 0.1%) and in post-marketing studies. In patients who develop RPLS, discontinue bevacizumab and initiate treatment of hypertension, if present. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurological sequelae. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is unknown.

K) Nasal septum perforation.
Reference: http://www.fda.gov/cder/Offices/OODP/whatsnew/bevacizumab200609.htm

V. CLINICAL MONITORING

A) Blood pressure every 2 – 3 weeks during treatment with bevacizumab. If increased blood pressure – perform BP monitoring more frequently.

B) Proteinuria: monitor for the development of proteinuria with serial urinalysis. Patients with ≥ 2+ protein on dipstick should have further assessments performed i.e., 24 hour urine collection.

VI. DRUG INTERACTIONS

No formal studies have been performed. There is no effect on the PK of irinotecan (parent compound), but there is a 33% increase in the concentration of the active metabolite SN-38.

CETUXIMAB
(ERBITUX™)

I. MECHANISM OF ACTION

Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody. Cetuximab binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands such as transforming growth factor-alpha. The EGFR is constitutively expressed in many normal epithelial tissues including the skin and hair follicle. Over expression of EGFR is detected in many human cancers including those of the colon and rectum. Binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production.

II. PHARMACOKINETICS

A) The elimination half-life of cetuximab is 7 days.
B) Females have an intrinsic 25% lower clearance of cetuximab compared to males. No dose modifications should be made in females.
C) No dosage adjustments are required in renal and hepatic dysfunction.

III. DOSAGE AND ADMINISTRATION

Dose: Combination with irinotecan or monotherapy: 400 mg/m^2 as an initial loading dose infused over 2 hours; then 250 mg/m^2 as weekly maintenance dose infused over 60 minutes DO NOT ADMINISTER CETUXIMAB AS AN IV PUSH OR BOLUS (Maximum infusion rate should not exceed 5 mL/min).

Cetuximab must be administered with the use of a low protein binding 0.22 micron in-line filter.

Premed with a H_1 antagonist e.g., diphenhydramine (Benadryl) 50 mg.Patients should be monitored for at least 1 hour following administration (vital signs every 15 minutes). Longer observation periods may be required in those patients experience infusion reactions.

No dilution required. Supplied in 100mg/50mL vials. Flush the line with saline at the completion of the infusion.

Preparations of cetuximab in infusion containers are stable for up to 12 hours under refrigeration and up to 8 hours at room temperature.

IV. TOXICITY

A) Infusion Reactions: Infusion reactions occurred with the administration of cetuximab in 11% of patients receiving cetuximab monotherapy and 19% in patients receiving cetuximab plus irinotecan. Severe infusion reactions occurred with administration of cetuximab in approximately 3% of patients (rarely fatal <1 in 1000). Approximately 90% of severe infusion reactions were associated with first infusion. Severe infusion reactions characterized by rapid onset of airway obstruction (bronchospasm, stridor, and hoarseness), urticaria, and hypotension have been reported. Incidence of fever associated with cetuximab has been reported as 37%. Severe infusion reactions require immediate interruption of infusion and permanent discontinuation from further treatment. If patients have a Grade 1/II infusion reaction, decrease the infusion rate by 50% permanently. If Grade III/IV toxicity occurs, then discontinue cetuximab therapy permanently.

B) Dermatological toxicities including acneform rash have been reported. In clinical studies, patients with advanced colorectal cancer, acneform rash was reported in 88% of all treated patients, and were severe (grade 3 or 4) in 12%. The acne-like rash associated with cetuximab appears to be a sterile, suppurative form of folliculitis, which commonly starts on the face, scalp, chest, and upper back. It usually occurs within the first 3 weeks of treatment and then stabilizes or resolves with continued therapy.

It is recommended that patients wear sunscreen and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reaction. It has been reported that treatment of the rash with topical or oral antibiotics, topical hydrocortisone, and/or retinoids does not provide consistent clinical benefit.

Severe acneform rash	Cetuximab	Outcome	Cetuximab Dose Modification
1st occurrence	Delay infusion 1-2 weeks	Improvement No improvement	Continue at 250 mg/m^2 Discontinue cetuximab
2nd occurrence	Delay infusion 1-2 weeks	Improvement No improvement	Reduce dose to 200mg/m^2 Discontinue cetuximab
3rd occurrence	Delay infusion 1-2 weeks	Improvement No improvement	Reduce dose to 150mg/m^2 Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

When cetuximab is used in conjunction with radiation, there is a much higher incidence of rash (95% in one lung cancer trial), with 19% patients developing a Grade III rash. The incidence and severity of cutaneous reactions with combined modality therapy appears to be additive, particularly within the radiation port.

C) Asthenia is frequent during cetuximab administration, occurring in up to 49% of patients receiving cetuximab monotherapy and 73% of patients receiving cetuximab plus irinotecan; it does not appear dose-related and is usually not severe.

D) Interstitial lung disease (ILD) was reported in <0.5% of patients with advanced colorectal cancer receiving cetuximab. Interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in one case.

V. CLINICAL MONITORING:

A) A 1-hour observation period is recommended following the cetuximab infusion. Longer observation periods may be required in patients who experience infusion reactions.

B) Patients should be periodically monitored for hypomagnesemia, and accompanying hypocalcemia and hypokalemia, during and following the completion of cetuximab therapy. Monitoring should continue for a period of time commensurate with the half-life and persistence of drug in the body i.e., 8 weeks [Reference: FDA Safety warning].

GEMTUZUMAB
(MYLOTARG™)

I. MECHANISM OF ACTION

Gemtuzumab is composed of a recombinant humanized IgG, kappa antibody conjugated with a cytotoxic antitumor antibiotic, calichaemicin, isolated from fermentation of a bacterium, *Micromonospora echinospora*. Gemtuzumab binds to the CD33 antigen expressed by hematopoietic cells. This binding of the anti-CD33 antibody portion of the gemtuzumab with the CD33 antigen causes the formation of a complex that is internalized. Once it is internalized the calicheamicin is released resulting in DNA strand breaks/cell death.

I. PHARMACOKINETICS

Gemtuzumab ozogamicin is given intravenously. Following a 2-hour infusion, the elimination half-lives of total and unconjugated calicheamicin are about 45 and 100 hours, respectively. After administration of a second dose 14 days later, the half-life of total calicheamicin is increased to about 60 hours and the AUC is about twice that in the first dose period. The pharmacokinetics of the unconjugated calicheamicin does not appear to change after the second dose. Hydrolytic enzymes are responsible for the release of calicheamicin from gemtuzumab ozogamicin. Many metabolites of calicheamicin have been found during *in vitro* incubation of gemtuzumab ozogamicin with human liver micosomes and cytosol or with HL-60 promyelocytic leukemia cells. Metabolic studies characterizing the possible hepatic microsomal isoenzymes involved in the metabolism of gemtuzumab ozogamicin have not been performed.

II. DOSAGE AND ADMINISTRATION

A) Given 9 mg/m^2 IV over 2 hours every 14 days times 2 doses (dose on ideal body weight). Some studies now giving second dose on day 4. NOTE: some protocols (i.e., ECOG 1900) use lower doses (6 mg/m^2) of gemtuzumab.
B) Dilute in 100 mL NS.
C) Premed with diphenhydramine (Benadryl®) and acetaminophen (Tylenol®).
D) May be administered in an outpatient setting. Vital signs should be monitored during the infusion and for fours hours following infusion.

III. TOXICITY

A) Infusion related such as fever and chills. Generally occur after the end of the 2-hour infusion and resolve 2 to 4 hours with supportive care.
B) Myelosuppression in 98% with recovering ANC to 500 x 10^9/L by a median of 40.5 days after the first dose. Thrombocytopenia in 99% and anemia in 47%.
C) Hepatotoxicity- abnormalities in liver function are transient and reversible. Hepatotoxicity, including severe hepatic veno occlusive disease (VOD), has been reported in association with the use of gemtuzumab as a single agent, as part of a combination chemotherapy regimen, and in patients without a history of liver disease or undergoing hematopoietic stem cell transplantation [References: *Cancer* 2001;92:406 - 13; *Bone Marrow Transplant*. 2002;3:23 - 8; *Blood*. 2002 Apr 1;99:2310 - 4; *Clin Lymphoma*. 2002 Suppl 1:S35 - 9].
D) Mucositis.
E) Tumor lysis syndrome has been reported to occur with gemtuzumab. Appropriate precautions should be taken.

IV. CLINCIAL MONITORING: Monitor CBC and differential; LFT's.

Last Updated on January 15, 2007

PANITUMUMAB
(VECTIBIX™)

I. MECHANISM OF ACTION

Panitumumab is a recombinant, human IgG2 kappa monoclonal antibody that binds to the human epidermal growth factor receptor (EGFR or erbB1), leading to inhibition of EGFR activation. EGFR is a transmembrane glycoprotein that promotes cell growth in a variety of normal and transformed tissues and is expressed in several solid tumors. Panitumumab blocks EGFR binding of the ligands epidermal growth factor (EGF), transforming growth factor alpha (TGFα), amphiregulin, betacellulin, epiregulin, and heparin-binding EGF.

II. PHARMACOKINETICS

Panitumumab exhibits nonlinear PK across most populations. The clearance decreases with increasing dose. The half-life increased with increasing dose from 12 hours at doses of less than 1 mg/kg to approximately 24 hours for doses greater than 1 mg/kg and to 96 hours for doses greater than 2 mg/kg. The non-linear clearance is thought to occur as a result of progressive saturation of EGFR. The dose that has been most studied is 2.5 mg/kg and at this dose the half-life is 6 days. Steady-state levels are reached by the 3rd infusion. Pharmacokinetics of panitumumab are not affected by: age (21 – 88 years), gender, race, mild-to-moderate renal dysfunction, mild-to-moderate hepatic dysfunction, and EGFR membrane-staining intensity (1+, 2+, 3+) in tumor cells. No formal studies have been conducted in patients with renal or hepatic impairment. Panitumumab has not been evaluated in children.

III. DOSAGE AND ADMINISTRATION:

The dose schedule most extensively evaluated is 2.5 mg/kg weekly. Clinical trials evaluating 6 mg/kg every 2 weeks are ongoing.

IV. TOXICITY

A) Dermatologic: the most frequent adverse event is a skin rash. Dermatological toxicity was reported in 89% of patients and severe (NCI CTC Grade 3 and higher) occurred in 12% patients receiving panitumumab monotherapy. The clinical manifestations include, but are not limited to, dermatitis acneiform, pruritis, erythema, rash, skin exfoliation, paronychia, drug skin, and skin fissures. The drug should be withheld in patients with severe dermatologic toxicity.

B) Infusion related adverse events: the incidence of infusion-related adverse events is small (less than 1%) and premedication is not necessary with this agent. If a severe reaction occurs (anaphylactic reactions, bronchospasm, hypotension), stop the infusion.

C) Diarrhea: panitumumab can cause diarrhea, and when coadminstered with irinotecan-containing regimens increases the incidence and severity of chemotherapy-induced diarrhea.

D) Electrolyte abnormalities: hypomagnesemia has been reported with this agent in up to 38% of patients (3% were Grade 3 or 4). Other common side effects include abdominal pain, fatigue, nausea and diarrhea.

E) Pulmonary fibrosis: occurred in less than 1% patients. Permanently discontinue panitumumab in patients who develop interstitial lung disease, pneumonitis, or lung infiltrates.

V. CLINICAL MONITORING

Evaluate the patient throughout the infusion for infusion-related adverse events. Examine the patient's skin for dermatologic toxicity.

VI. DRUG INTERACTIONS

Concomitant administration of panitumumab with paclitaxel and carboplatin does not affect the PK of panitumumab nor the PK of the antineoplastic agents. Similarly the concomitant administration of panitumumab and irinotecan does not affect either drug.

RITUXIMAB
(RITUXAN®)

I. MECHANISM OF ACTION

Rituximab is a genetically engineered mouse/human antibody directed against the CD20 antigen on the surface of normal and malignant B-lymphocytes. It is an IgG type antibody with mouse variable region and human constant region. It is produced in a Chinese hamster ovary system. When rituximab binds to the CD20 antigen, it induces complement fixation and cell lysis. There is rapid disappearance of B-lymphocytes from peripheral blood and tissues. Up to three doses may be necessary to irradicate the B cells, but the effect may last up to 6 to 9 months.

II. PHARMACOKINETICS

Distribution to thymus, spleen, and lymph nodes. The mean serum elimination half-life after the first rituximab infusion is 76.3 hours (range: 31.5—152.6 hours); the half-life after the fourth infusion is about 205.8 hours (range: 83.9—407 hours). The wide range of half-lives may be related to the variable tumor burden among patients and the changes in CD20+ B-cell populations upon repeated administration. The median time to onset of response is about 50 days, and the median duration of response is projected to be 10—12 months. Upon completion of a treatment course, rituximab can be detected in a patient's serum for about 3—6 months.

III. DOSAGE AND ADMINISTRATION

A) Given as 375 mg/m^2 weekly for four doses only [NOTE: higher doses have been studied, up to 2250 mg/m^2, but in small numbers of patients with limited outcome data].
B) Please round the dose to the nearest 100 mg.
C) Dilute in NS or D_5W to 1 - 4 mg/mL.
D) Premedicate prior to each dose (See Premedication section). This may reduce infusion reactions. Consider Hydrocortisone 50 - 100 mg prior to first dose.
E) Administer the first dose at an initial rate of 50 mg/hr. If no hypersensitivity or infusion related events occur escalate the infusion in 50 mg/hr increments every 30 minutes, to a max of 400 mg/hr. Subsequent doses should/can start at 100 mg/hour provided there were no reactions on the first doses. The rate can then be increased to a maximum of 400 mg/hr.

IV. TOXICITY

A) Infusion related reactions such as rigors and chills.
B) Hypogammaglobulinemia without increased incidence of infection.
C) Severe thrombocytopenia, granulocyte deficiency, and anemia in 1-2% of patients.
D) Hypersensitivity reactions, hypotension, angioedema, and bronchospasm. Stop infusion, administer methyprednisolone, and restart at 50% of the original rate.
E) Mucocutaneous reactions (Black Box Warning) – mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with rituximab. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy), Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1 - 13 weeks following rituximab therapy. Patients that experience a severe mucocutaneous skin reaction should not receive any further infusions [Reference: Genentech/IDEC Safety Information Letter, May 8, 2001].
F) Atypical infections have been reported, such as tuberculosis.

G) Hepatitis B virus reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematological malignancies treated with rituximab. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituxumab and approximately 1 month after the last dose.

V. CLINICAL MONITORING:

Patients at high risk for hepatitis B infection should be screened before the initiation of rituxumab therapy. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active hepatitis B infection and for signs of hepatitis during and for up to several months following rituximab therapy. In patients who develop viral hepatitis, rituximab and any concomitant chemotherapy should be discontinued and appropriate treatment (including antiviral therapy) initiated.

TRASTUZUMAB
(HERCEPTIN®)

I. MECHANISM OF ACTION
Trastuzumab is a hybrid monoclonal antibody to the ER-2-neu protein over expressed on the surface of some breast cancers. It is a hybrid of murine and human IgG that leads to successful therapeutic activity without immunogenicity. It is produced in Chinese hamster ovary cells. Tumor cell proliferation is inhibited. Trastuzumab also is a mediator of antibody dependent cell-mediated cytotoxicity via natural killer cells and monocytes.

II. PHARMACOKINETICS
Administer IV. Has a half-life of 5.8 days but ranges from 1-32 days. Distribution and clearance are not well described, but renal dysfunction does not appear to impair its clearance.

III. DOSAGE AND ADMINISTRATION
LD of 4 – 8 mg/kg in 250 mL NS over 90 min. Maintenance dose is either 2 mg/kg IV or 6 mg/kg in 250 mL NS over 30 min. NOTE: lower doses are administered weekly and the larger doses are administered every 3 weeks – see individual drug regimens. If given with paclitaxel, give trastuzumab first and paclitaxel 24 hr later. If no adverse reaction then paclitaxel may be given immediately after trastuzumab on future courses. Premedicate.

IV. TOXICITY
A) Cardiomyopathy-seen with combination therapy with anthracyclines. Incidence=19%. (Reference: Perez E, et al. J Clin Oncol 2004;22:322 – 9). Trastuzumab can result in the development of ventricular dysfunction and CHF. LV function should be evaluated in all patients prior to and during treatment with trastuzumab. Discontinuation of trastuzumab should be strongly considered in patients who develop a clinically significant decrease in LV function. In the NSABP B-31 trial 30.5% patients randomized to the trastuzumab arm developed asymptomatic decreases in LVEF or cardiac symptoms. In 18.6% patients, trastuzumab was discontinued prior to the completion of 1 year of therapy because of asymptomatic decreases in LVEF (14.3%) and symptomatic cardiac dysfunction/other cardiac toxicity (4.3%). A statistically significant increase in the 3-year cumulative incidence of NYHA Class III and IV CHF and cardiac death was observed in patients who received the trastuzumab-containing regimen (4.1%) compared to control (0.8%). In the NSABP B-31 trail monitoring of LVEF occurred at baseline, and was repeated at the completion of AC and at 6, 9, and 18 months after the initiation of paxlitaxel with or without trastuzumab. Dose modification guidelines in this trial were as follows:

Relationship of LVEF to LLN	Absolute Decrease		
	< 10%	10 – 15%	≥ 16%
Within normal limits	Continue	Continue	Hold[a]
1 – 5% below LLN	Continue	Hold[a]	Hold[a]
≥ 6% below LLN	Continue	Hold[a]	Hold[a]

[a]Repeat LVEF assessment after 4 weeks. If criteria for continuation were met, trastuzumab was resumed. If 2 consecutive holds or total of 3 holds occurred, trastuzumab was discontinued.

Reference: FDA Safety Warning. See also section on Trastuzumab-related cardiotoxicity.

B) Infusion related reactions-fever, chills, nausea, dizziness, dyspnea, headache.
C) Maculopapular rash.
D) Pain, asthenia.
E) Diarrhea.
F) Peripheral edema, peripheral neuropathy, arthralgia.

V. CLINICAL MONITORING

Check an initial echocardiogram or MUGA scan prior to receiving any trastuzumab therapy for baseline. Reassess approximately every 3 months during the first year of therapy followed by every 6 months for 5 years then annually while on treatment or as clinically indicated.

References: Tan-Chiu E, et al. *J Clin Oncol* 2005;23:7811 - 9; Piccart-Gebhart MJ, et al. *N Engl J Med* 2005;353:1659 - 72; Romond E, et al. *N Engl J Med* 2005;353:1673 - 84.