Biologic Therapies—
Mechanisms of Action and
Treatment Considerations

Seth Eisenberg, RN, OCN®
Professional Practice Coordinator, Infusion Services
Seattle Cancer Care Alliance
Seattle, WA

CE Credit in Four Easy Steps!

1. Scan your badge as you enter each session.
2. Carry your Evaluation Packet to every session so you can add session evaluation forms to it.
3. Track your hours on the “Statement of Session Attendance Form” as you go.
4. At your last session, total the hours and sign both pages of your Statement of Session Attendance Form.
   ✓ Keep the PINK copy for your records.
   ✓ Put the YELLOW and WHITE copies in your CE Envelope.
   ✓ Make sure an Evaluation Form is in your CE Envelope for each session you attended.
   ✓ Miss one? Extras are in a file near Registration.
   ✓ Fill out the information on the outside of the CE Packet envelope, seal it, and drop it in the box near Registration.
   ✓ Applying for Pharmacy CPE? If you have not yet registered for an NABP e-Profile ID, please visit www.MCPeMonitor.net to do so before submitting your packet. You must enter your NABP e-Profile ID to receive CE credit this year!

Speaker Disclosures

Seth Eisenberg has no conflicts of interest or financial disclosures to declare.

Clinical trials and off-label/investigational uses will be discussed during this presentation in a fair and unbiased manner.
Chemotherapy Versus Biotherapy

- **Chemotherapy**
  - Affects rapidly dividing cells
  - Non-specific
  - Unable to differentiate between normal and malignant cells

- **Biotherapy**
  - Targets pathways, antigens, or surface markers on cells
  - Engineered to find a specific target
  - Can carry cytotoxic payload to a target

Not all targeted therapies are biologic

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Clinical Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (Gleevec)</td>
<td>Tyrosine kinase inhibitor</td>
<td>CML, GIST</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>Multiple kinase inhibitor</td>
<td>Renal Cell Cancer</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>VEGF inhibitor</td>
<td>Lung Cancer</td>
</tr>
<tr>
<td>Vismodegib (Erivedge)</td>
<td>Hedgehog inhibitor</td>
<td>Basal Cell Carcinoma</td>
</tr>
<tr>
<td>Luprolide Acetate (Lupron)</td>
<td>LH-RH analog</td>
<td>Prostate Cancer</td>
</tr>
</tbody>
</table>

General Characteristics

- Act directly on the immune system
- Mimic naturally occurring proteins
- Can be genetically engineered
- Enhance or block biologic pathways
- Target specific surface markers on cells
Examples of Indications

• Non-oncologic immune disorders
  – Crohn’s disease
  – Psoriasis
• Oncologic diseases
  – Lymphomas
  – Melanoma
  – Breast cancer
  – Prevention and treatment of Acute Graft Versus Host Disease
• Anti-viral
  – Hepatitis C

Targeted Therapy = Magic Bullet?

• Many agents can accurately reach their target
• Reaching target does not always equate with cure or achieving desired effect(s)
• Significant side-effects related to:
  – Complex up or down-regulation of pathways
  – Cytokine Release Syndrome
  – Unintentional blockade of desirable biologic mechanisms

Complex Signaling Pathways
When the target fights back

- 2006 Phase I study of TGN 1412
- CD28 MAb, able to active T-cells without prior activation of T-cell receptors
- Potential use for rheumatoid arthritis and lymphoma
- No anticipated side effects based on animal models

When the target fights back

- Given simultaneously to 6 healthy volunteers
- Within 1 hour after the infusion, all 6 became critically ill due to a “cytokine storm”
- Later analysis hypothesized the reaction was due to lack of CD28 expression on the CD4+ T-cells in animal models but is expressed in humans
Types of Biotherapy

- Cytokines
  - Interleukins
  - Interferons
  - Chemokines
  - Growth Factors
- Fusion Proteins
- Monoclonal Antibodies
  - Naked
  - Conjugated

Cytokines

- Polypeptide Proteins
- Chemical messengers
- Released transiently under normal circumstances
- Action
  - Autocrine (act on the cell which secreted it)
  - Paracrine (act on nearby cells) (e.g., IL-6, TGF-β in melanoma).
  - Endocrine (act on distance cells)

Cytokines

- Produced by lymphocytes, fibroblasts, endothelial cells, mast cells
- Stimulate the release of other cytokines (e.g., chemokines)
- Activate lymphocytes
- Increased production during times of emotional stress or during infection
- Utilize JAK-STAT and nuclear factor kappa β pathways
Cytokines

- Stimulate the production of
  - endothelial leukocyte adhesion molecule 1
  - vascular cell adhesion molecules
- Release
  - Prostaglandins (lipid compounds)
  - Leukotrienes (inflammatory mediators)
  - Proteases (proteolytic enzymes)
- Stimulation or inhibition of cytokines can have widespread effects due to interdependent pathways


Cytokines

- Many are pro-inflammatory:
  - IL-1 (considered the inflammatory gatekeeper)
  - IL-2
  - IL-6
  - TNFα
- Pro-inflammatory cytokines are implicated in a number of diseases:
  - Crohn’s disease
  - RA
  - Asthma
  - Psoriasis

Dinarello, C (2011)

Cytokines

- TGF-β can be pro-inflammatory or anti-inflammatory
  - Anti-inflammatory when
    - secreted in the gut (to protect GI flora)
    - promoting wound healing
  - Pro-inflammatory related to B-cell activation and numerous interleukin-dependent pathways
- IL-4 and IL-10 are anti-inflammatory

Cytokines

• Tumor Necrosis Factor (TNFα and TNFβ)
  – Primarily produced by macrophages
  – Role in
    • Inflammation
    • Immune system regulation and initial response to infection
    • Tumor growth and apoptosis inhibition
  – Potential antineoplastic therapy

Interferons

• Properties:
  – Immunomodulatory
  – Antiproliferative
  – Antiangiogenic
  – Antiviral
• 3 major subtypes differentiated by their target receptors
Interferons

• Type I: Alpha (α) and Beta (β)
  — Inhibit viral replication
  — Produced by hematopoietic progenitor cells and fibroblasts
• Type II: Gamma (γ)
  — Activates T-cells
  — Upregulates NK cells
  — Regulates B-cell function
• Type III: Lambda (λ) or IL-28A, IFN λ 2 or IL-28B, and IFN-λ 3 or IL-29
  — Modest antiviral activity

Interferon Pathways

• Modulate NK cells and macrophages
• Interact with cytokines:
  — IL-1
  — IL-2
  — IL-6
  — IL-8
  — TNF

FDA Approved Interferons

• 5 commercial products
• 4 are genetically engineered from Escherichia coli bacterium
• 1 (IFN alfa-n3) is derived from human leukocytes partially infected with the avian Sendai virus
FDA Approved Interferons

<table>
<thead>
<tr>
<th>IFN Subtypes</th>
<th>Route</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alpha-2a</td>
<td>SC</td>
<td>Hepatitis B and C</td>
</tr>
<tr>
<td>(Pegasys)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon alpha-2b</td>
<td>SC</td>
<td>Hairy cell leukemia, melanoma, sarcoma, hepatitis B &amp; C, AIDS-related Kaposi's</td>
</tr>
<tr>
<td>(Intron®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon alfa-n3</td>
<td>IL</td>
<td>Human papilloma virus genital warts</td>
</tr>
<tr>
<td>(Alferon N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon beta-1b</td>
<td>SC</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>(Betaseron®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon gamma-1B</td>
<td>SC</td>
<td>Chronic granulomatous disease, and malignant osteoporosis</td>
</tr>
<tr>
<td>(Actimmune)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interferon side effects

- Flu-like symptoms (fever, chills, headache, fatigue)
  - Premed with acetaminophen
- Capillary Leak Syndrome
- Neurologic/Psychiatric (neuropathy, confusion, anxiety, depression, suicidal behavior)
  - Premedication with paroxetine can be beneficial
- Myelosuppression
- Infection
- Injection site reactions

Interleukins (ILs)

- A family of glycoproteins
- 37 different ILs produced in the human body
- IL-1: proinflammatory cytokine
  - Referred to as the cytokine "gatekeeper"; implicated in RA, psoriasis
- IL-2: proinflammatory cytokine
  - Causes proliferation of T and B cells, differentiation of NK cells; implicated in x-linked SCID
### IL-1: Inflammatory Gatekeeper

<table>
<thead>
<tr>
<th>Physiologic</th>
<th>Inflammatory</th>
<th>Hematologic</th>
<th>Immunologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>↑ COX-2</td>
<td>↑ Neutrophils</td>
<td>B-cell activation</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>↑ VEGF</td>
<td>↑ Phagocytosis</td>
<td>T-cell activation</td>
</tr>
<tr>
<td>Shock</td>
<td>↑ Chemokines</td>
<td>↑ GCSF</td>
<td>NK cell activation</td>
</tr>
<tr>
<td></td>
<td>↑ TNF</td>
<td>↑ IL-6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ IL-2</td>
<td>↑ Fibroblasts</td>
<td></td>
</tr>
</tbody>
</table>

Dinarello, C (2011)

### FDA Approved Interleukins

- **IL-2 Aldesuken**
  - Proleukin®
- **IL-11 Oprelvekin**
  - Neumega™
- **IL-1 Antagonist Anakinra**
  - Kineret®

### IL-2 Proleukin®

- A recombinant lymphokine
- Stimulates endogenous production of
  - Natural Killer Cells (NK)
  - Cytotoxic T Cells (CTC)
  - Lymphokine Activated Kinase (LAK) Cells, Macrophages
- IL-4
- IL-5
- IL-6
IL-2 Proleukin®

- Administered IV
- Indicated for the treatment of
  - metastatic melanoma
  - renal cell cancer

IL-2 Proleukin®

- Side effects:
  - Hypotension
  - Fluid retention
  - Capillary leak syndrome
  - Pulmonary edema
  - Flu-like symptoms (fever, chills, malaise)
  - Depression
  - Exacerbation of pre-existing autoimmune diseases
  - Delayed reaction to iodinated contrast media

IL-11 Neumega™

- A thrombopoietic growth factor
- Stimulates the proliferation of stem cells and megakaryocytes to increase platelet production
- Administered SC
- Indicated for the prevention of severe thrombocytopenia in high-risk patients receiving chemotherapy
IL-11 Neumega™

- Side effects:
  - Anaphylaxis (with subsequent doses)
  - Atrial arrhythmias
  - Pulmonary edema
  - Dyspnea
  - Peripheral edema
  - Capillary leak syndrome
  - Potentially fatal hypokalemia

IL-1 antagonist Kineret®

- Modified form of human interleukreceptor antagonist (IL-1Ra)
- Competitively inhibits IL-1 binding to the IL-1 receptor
- Administered SC
- Indicated for reducing symptoms of moderate to severe rheumatoid arthritis

IL-1 antagonist Kineret®

- Side Effects:
  - Injection site reactions
  - Infection
  - 3.6x higher risk of lymphoma
### IL-1 Properties

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Hematologic</th>
<th>Immunologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ COX-2</td>
<td>↑ Neutrophils</td>
<td>B-cell activation</td>
</tr>
<tr>
<td>↑ VEGF</td>
<td>↑ Phagocytosis</td>
<td>T-cell activation</td>
</tr>
<tr>
<td>↑ Chemokines</td>
<td>↑ GCSF</td>
<td>NK cell activation</td>
</tr>
<tr>
<td>↑ TNF</td>
<td>↑ IL-6</td>
<td></td>
</tr>
<tr>
<td>↑ IL-2</td>
<td>↑ Fibroblasts</td>
<td></td>
</tr>
</tbody>
</table>

### Chemokines

- 52 naturally occurring chemokines have been identified
- Specialized cytokines that produce chemotaxis (cell migration) in
  - Neutrophils
  - Lymphocytes
  - Fibroblasts
  - Keratinocytes
- Activate white blood cells (inflammatory response)
- Assist with immune surveillance and hematopoiesis

### Plerixafor (Mozobil®)

- Inhibits the CXCR4 chemokine receptor and blocks binding of its stromal cell-derived factor-1α (SDF-1α)
- CXCR4 helps anchor stem cells to the marrow matrix
- Administered SC
- Indicated for enhancing peripheral blood stem cell mobilization in conjunction with GCSF (filgrastim) for
  - Multiple myeloma
  - Non-Hodgkin’s lymphoma
Plerixafor (Mozobil®)

- Side effects:
  - Injection site reactions
  - Nausea/Vomiting
  - Diarrhea
  - Fatigue
  - Headache

Fusion Proteins

- Consist of a protein component (i.e., IgG) plus an immunotoxin or cytokine agonist / antagonist
- Examples:
  - Etanercept
  - Romiplostim
  - Denileukin diftitox

Etanercept (Embrel®)

- Tumor necrosis factor receptor (TNFR) fusion protein which blocks TNF-α and TNF-β
- TNF-α plays a role in
  - chronic inflammatory diseases
  - normal immune protection
Etanercept (Embrel®)

- Administered SC
- Indicated for:
  - Moderate to severe rheumatoid arthritis
  - Plaque psoriasis
  - Psoriatic or Juvenile Idiopathic Arthritis
  - Ankylosing spondylitis

Etanercept (Embrel®)

- Side effects:
  - Injection site reactions
  - Severe infection
  - Potentially permanent central nervous system demyelinating disorders
  - Increased mortality in patients with cardiac disease
  - 3x higher risk of lymphoma

Romiplostim (Nplate™)

- An Fc-peptide fusion protein
- Increases platelet production by activating thrombopoietin (TPO) cytokine receptor pathways
- FDA approved for the treatment of ITP (idiopathic thrombocytopenic purpura) in patients at high risk of bleeding
Romiplostim (Nplate™)

- Administered SC
- Side effects:
  - Bone marrow reticulin deposition
  - Thromboembolism
  - Increased risk of hematologic malignancy
  - Headache, dizziness, insomnia
- Restricted distribution

---

Denileukin diftitox (Ontak®)

- CD25-directed fusion protein conjugated with diphtheria toxin
- Administered IV
- Indicated for persistent or recurrent cutaneous T-cell lymphoma expressing the CD25 component of the IL-2 receptor

---

Denileukin diftitox (Ontak®)

- Side effects:
  - Capillary leak syndrome (common)
  - Fever and chills
  - Nausea and vomiting
  - Rash
- Fewer reactions seen with subsequent doses
Monoclonal Antibodies

- Immunoglobulins which target cell surface antigens
- Consist of 4 polypeptides:
  - Two heavy chains
  - Two light chains
- The variable region provides antigen specificity
- The constant region determines the mechanism for destroying the antigen
Monoclonal Antibodies

• Target a specific antigen (e.g., CD20) (CD = Clusters of Differentiation)
• Monoclonal antibodies are exact copies of a single genetically engineered clone
• This allows for the production of large quantities of antibodies

Monoclonal Antibodies

• Initially only produced using murine hybridoma technology
• First commercial MAb (1985) muromonab (OKT3)
• Can be “naked” or conjugated
• Produced in Chinese Hamster Ovaries (CHO)
• Most newer mAbs are humanized or fully human

Naming Conventions

• The type or source can be identified by the middle syllable in the generic name

<table>
<thead>
<tr>
<th>Gen</th>
<th>Murine</th>
<th>Type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>100%</td>
<td>Fully murine</td>
<td>Tositu-mo-mab (-mo)</td>
</tr>
<tr>
<td>II</td>
<td>25%</td>
<td>Chimeric</td>
<td>Ritu-xi-mab (-xi)</td>
</tr>
<tr>
<td>III</td>
<td>15%</td>
<td>Humanized</td>
<td>Trastu-zu-mab (-zu)</td>
</tr>
<tr>
<td>IV</td>
<td>0%</td>
<td>Fully human</td>
<td>Panitu-mu-mab (-mu)</td>
</tr>
</tbody>
</table>
Conjugated Monoclonal Antibodies

- Linked to a pharmaceutical toxin or radioactive isotope
- Deliver “payload” directly to targeted cell
- Examples:
  - Gemtuzumab ozogamicin* (Mylotarg™)
  - Brentuximab vedotin (Adcetris™)
  - Ibritumomab tiuxetan (Zevalin™)

* Withdrawn from market in 2010
25 Commercially Available mAbs

<table>
<thead>
<tr>
<th>Name</th>
<th>Other Name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abicizimab</td>
<td>Bivalent mAb</td>
</tr>
<tr>
<td>Abilumab</td>
<td>Trellembol</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Avastin</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Tarceva</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Zenapax</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Prolia</td>
</tr>
<tr>
<td>Ecluzumab</td>
<td>Eculizumab</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Tarceva</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Xolair</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
</tr>
<tr>
<td>Melimumab</td>
<td>Parlimumab</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Tysabbi</td>
</tr>
<tr>
<td>Palivizumab</td>
<td>Synagis</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Vectibix</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Taxotere</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Perjeta</td>
</tr>
<tr>
<td>Pembrolizum</td>
<td>Libtayo</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituxan</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Arthran</td>
</tr>
<tr>
<td>Tositumomab</td>
<td>Zevalin</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
</tr>
<tr>
<td>Tuximab</td>
<td>Tysabbi</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Stelara</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Vincriabin</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Vincaleustine</td>
</tr>
</tbody>
</table>

Approved Indications

**Autoimmune**
- Rheumatoid arthritis
- Chronic lymphocytic leukemia
- Connective tissue disease
- Juvenile idiopathic arthritis

**Oncology**
- Breast cancer
- Colorectal cancer
- Gastric cancer
- Melanoma
- Non-small cell lung cancer
- Squamous cell carcinoma

**Other**
- Ankylosing spondylitis
- Crohn's disease
- Dermatomyositis
- Graft-versus-host disease
- Hurler's syndrome
- Idiopathic thrombocytopenic purpura
- Juvenile idiopathic arthritis
- Kawasaki disease
- Myelodysplastic syndrome
- Multiple myeloma
- Paroxysmal nocturnal hemoglobinuria

To be effective, the mAb must
- Avoid immune clearance
- Identify and bind to the target
- Destroy the cell expressing the antigen, or recruit other cells
- Be able to unlink the payload from conjugated mAbs
Monoclonal Antibodies

COMMON SIDE EFFECTS

3/27/2013

Allergic hypersensitivity

- IgE-mediated reactions, usually to the non-human portion
- Requires prior exposure (although cross-reactivity has been demonstrated with cetuximab)
- Causes the release of histamine, leukotrienes, and prostaglandins and the degranulation of mast cells
- Results in symptoms of anaphylaxis:
  - smooth muscle contraction
  - capillary dilation with increased vascular permeability
  - urticaria and rash,
  - angioedema, bronchospasm, and hypotension

O’Neil, B (2007)

Cytokine Release Syndrome (CRS)

- Can be mild or potentially fatal (cytokine storm)
- Caused by release of both endogenous cytokines and those from damaged tumor cells
  - TNF-α
  - IFN-γ
  - IL-8
  - IL-6
- Symptoms are very similar to allergic reactions and may be difficult to differentiate

Chung, C (2008); Vulturgo, A et al (2011)
Cytokine Release Syndrome (CRS)

- Reaction rates for same drug can vary depending on
  - specific disease
  - disease burden
- Decreases with subsequent doses
  - Reactions to subsequent dose of trastuzumab are very rare

CRS Symptoms

- Hypersensitivity reactions
- Arthalgias
- Bronchospasm, cough or dyspnea
- Fever and chills
- Fatigue
- Hypertension, hypertension, tachycardia
- Nausea/vomiting
- Dermatologic manifestations (pruritus, rash)

Prevention

- Premedication
  - Diphenhydramine
  - Acetaminophen
  - Steroids
General Interventions

- Stop the infusion
- Get help
- Assess ABCs
- Maintain vascular access with normal saline
- Obtain order for:
  - Diphenhydramine
  - A corticosteroid
  - Epinephrine
- Monitor vital signs (including oxygen saturation)

SELECTED MONOCLONALS
Rituximab (Rituxan®)

- First widely successful mAb
- Targets CD20 positive B lymphocytes
- The Fab domain binds to the CD20 antigen and the Fc domain recruits cytotoxic cells
- Indicated for
  - Lymphoma
  - CLL
  - RA

Rituximab (Rituxan®)

- Administered IV
- First dose slow titration
- Infusion reactions (77% of first doses) but can be disease dependent
- Several published studies now demonstrate the safety of 60-90 minute rituximab infusions for subsequent doses

Alemtuzumab (Campath®)

- Targets CD52 positive B lymphocytes
- Binds to healthy T cells, B cells, NK cells, and granulocytes
- Indicated for Chronic Lymphocytic Leukemia
- Administered IV by increasing subsequent doses until maximum is reached
Alemtuzumab (Campath®)

- **Side effects:**
  - Infusion reactions (89% of first doses)
  - Serious fatal infections due to severe prolonged cytopenias
  - Requires prophylaxis for PCP and herpes

Trastuzumab (Herceptin®)

- **Anti HER2-neu mAb**
- **Indicated for treatment of HER2-neu positive breast and gastric cancer**
- **Administered IV**
- **Side effects:**
  - Congestive heart failure
  - Initial dose infusion reactions (fever, chills, n/v)
  - Pulmonary toxicity

Cetuximab (Erbitux®)

- **An epidermal growth factor receptor (EGFR) antagonist**
- **Administered IV**
- **Indicated for treatment of colorectal and head & neck cancer**
- **Side effects:**
  - Infusion reactions (up to 22% despite premedication)
  - Higher reaction rates in some states including Tennessee and N. Carolina
  - Acneform rash (88%)
  - Cardiopulmonary arrest
  - Test-doses may be of some clinical use
Bevacizumab (Avastin®)

- A vascular endothelial growth factor (VEGF) –specific angiogenesis inhibitor
- Indicated for:
  - metastatic colorectal cancer
  - lung cancer
  - glioblastoma
  - metastatic renal cell cancer
- Administered IV

Bevacizumab (Avastin®)

- Side effects:
  - Epistaxis
  - Headache
  - Hypertension
  - Impaired wound healing
  - Proteinuria
  - Taste alteration
  - Dry skin

Brentuximab vedotin (Adcetris®)

- CD30 antibody conjugate with the chemotherapeutic agent MMAE (monomethyl auristatin E)
- Indicated for:
  - Hodgkin’s lymphoma for patients who have failed ASCT or 2 other therapies
  - Large cell lymphoma after failure of 1 multi-drug regimen
- Administered IV
Brentuximab vedotin (Adcetris®)

- Side effects:
  - Neuropathy (sensory and peripheral)
  - Anaphylaxis
  - Neutropenia
  - Fatigue
  - URI
  - Nausea/Vomiting/Diarrhea
  - Rash
  - Tumor lysis syndrome

Ipilimumab (Yervoy™)

- Human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody
- Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation
- Indicated for unresectable or metastatic melanoma
- Administered IV

Ipilimumab (Yervoy™)

- Side effects:
  - Life-threatening enterocolitis with severe diarrhea
  - Immune-mediated dermatitis (e.g., Stevens-Johnson Syndrome, TEN)
  - Immune-mediated hepatitis
  - Fatigue

Package Insert
Panitumumab (Vectibix®)

• An epidermal growth factor receptor antagonist
• Indicated for metastatic colorectal carcinoma
• Administered IV
• Side effects:
  – Dermatologic toxicities (90%) [includes acneform rash]
  – Infusion reactions (~4%) [pre-medication is not indicated]
  – Hypomagnesemia

Infliximab (Remicade®)

• Binds with TNFα and inhibits TNFα and receptors
• Indicated for:
  – Crohn’s disease
  – Ulcerative colitis
  – Rheumatoid arthritis, Psoriatic arthritis
  – Ankylosing spondylitis
  – Plaque psoriasis

Infliximab (Remicade®)

• Administered IV
• Side effects:
  – Serious infection
  – Increased risk of lymphoma and other malignancies
  – Hepatotoxicity and HEP B reactivation
  – Hypersensitivity reactions
  – Serum sickness
  – Increased mortality in patients with pre-existing CV disease
Denosumab (Xgeva™)

• RANK ligand (RANKL) inhibitor
• Indicated for prevention of skeletal-related events in patients with bone metastases
• Administered SC
• Side effects:
  – Severe hypocalcemia
  – Osteonecrosis of the jaw

Summary

• Biologic Therapy includes a diverse group of agents
• Proven efficacy for malignant and non-malignant diseases
• Produce a variety of potentially lethal and serious non-lethal side effects