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.MyCPEmonitor.net to do so **before** submitting your packet. You must enter your NABP e-Profile ID in order 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 discussed during this presentation in a fair an 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>Sorafinib (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
RANKL Signaling Pathway

www.wikipathways.org/index.php/Pathway:WP382
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
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 (TNF$\alpha$ and TNF$\beta$)
  – Primarily produced by macrophages
  – Role in
    • inflammation
    • Immune system regulation and initial response to infection
    • Tumor growth and apoptosis inhibition
  – Potential antineoplastic therapy
TRAIL

- TNF-related apoptosis-inducing ligand (TRAIL)
  - Traditional chemotherapy induces apoptosis via the intrinsic pathway, which can result in resistance
  - Extrinsic pathway promotes apoptosis in cancer cells (sparing normal cells)
  - Exploits “death receptors” on cell surface
  - TRAIL can be potentiated by certain agents, including the proteasome inhibitor bortezomib

Sayers, T (2011); Wu GS (2009).
Interferons

• Properties:
  – Immunomodulatory
  – Antiproliferative
  – Antiangiogenic
  – Antiviral

• 3 major subtypes differentiated by their target receptors

Wilkes, G (2010); Coondoo, A (2011)
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 (Pegasys)</td>
<td>SC</td>
<td>Hepatitis B and C</td>
</tr>
<tr>
<td>Interferon alfa-2b (Intron® A)</td>
<td>SC</td>
<td>Hairy cell leukemia, melanoma, sarcoma, hepatitis B &amp; C, AIDS-related Kaposi's</td>
</tr>
<tr>
<td>Interferon alfa-n3 (Alferon N)</td>
<td>IL</td>
<td>Human papilloma virus genital warts</td>
</tr>
<tr>
<td>Interferon beta-1b (Betaseron®)</td>
<td>SC</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Interferon gamma-1B (Actimmune)</td>
<td>SC</td>
<td>Chronic granulomatous disease, and malignant osteoporosis</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>Inflammation</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) 3/27/2013
FDA Approved Interleukins

• IL-2 Aldesleukin
  – 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 diffitox
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 diffitox (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
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>
Monoclonal Antibodies

- Chimeric (25%) (rituximab)
- Humanized (15%) (trastuzumab)
- Human (panitumumab)

Murine portion  Human portion

©2011 S.Eisenberg
Types of MABs by year

Eisenberg, S (2012); Data from Nelson, AL (2010)
Conjugated Monoclonal Antibodies

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

* Withdrawn from market in 2010
25 Commercially Available mAbs

<table>
<thead>
<tr>
<th>Abicizimab</th>
<th>Ibritumomab tiuxetan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Infliximab</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Ipilimumab</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Natalizumab</td>
</tr>
<tr>
<td>Melimunab</td>
<td>Ofatumumab</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Palivizumab</td>
</tr>
<tr>
<td>Brentuximab vendotin</td>
<td>Panitumumab</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Tositumomab</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Ecluzumab</td>
<td>Ustekinumab</td>
</tr>
<tr>
<td>Golimumab</td>
<td></td>
</tr>
</tbody>
</table>

Eisenberg, S (2012)
**Approved Indications**

<table>
<thead>
<tr>
<th>Autoimmune</th>
<th>Oncology</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Chronic lymphocytic lymphoma</td>
<td>Cardiac ischemic prophylaxis</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Melanoma</td>
<td>Renal transplant rejection</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>Renal Cell cancer</td>
<td>Skeletal-related events (metastatic)</td>
</tr>
<tr>
<td>Plaque arthritis</td>
<td>Colorectal cancer</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Breast cancer</td>
<td>Atypical hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>Non-small cell lung cancer</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Glioblastoma</td>
<td>RSV prophylaxis</td>
</tr>
<tr>
<td>Asthma</td>
<td>Hodgkin’s lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low grade follicular lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastric cancer</td>
<td></td>
</tr>
</tbody>
</table>

Eisenberg, S (2012)
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
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
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); Vultaggio, 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

Lisander, J (2011); Atmar, J (2010); Lang, D (2011); Lang, D (2012); Chiang, J (2010); Al Zahrani, A (2009); Tuthill, M (2009)
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)
Epinephrine
Position Patient
Administer Oxygen
Administer IV Fluids
Administer Nebulizer
Administer vasopressors, antihistamines or corticosteroids

“Anaphylaxis pyramid”
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

Lisander, J (2011); Atmar, J (2010); Lang, D (2011); Lang, D (2012); Chiang, J (2010); Al Zahrani, A (2009); Tuthill, M (2009)
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
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