Intro to Immunotherapy: CAR T Cells, Checkpoint Inhibitors, BiTEs, Vaccines, Monoclonal Antibodies

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Clinical Director of Plasma Cell Disorders
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Overview

Immunotherapies:
1. Immune Checkpoint Inhibitors
2. Chimeric Antigen Receptor T-Cells (CAR T)
3. Bi-specific T-cell Engagers (BiTEs)
4. Monoclonal antibodies (mAb)

Other Immunotherapy (not covered today): Allogenic hematopoietic cell transplantation; Vaccine therapy
Role of Immune System

• Primary role: Protect the body from pathogens

• Immune surveillance: Detect and remove **aberrant cells**, including cancer cells

• T-cells (lymphocytes) recognize **aberrant** proteins present on cancer cells to coordinate an immune response
Key To Immunotherapy

• Most non-immunotherapies (ie convention chemotherapy) act directly on cancer cells
  – Inhibit tumor growth
  – Apoptosis
  – Impair cell division
  – Affect angiogenesis
Key To Immunotherapy

- Immunotherapy modulates the patient’s own immune system
  - Enhanced T-cell response (BiTEs; CAR T)
  - Antibody stimulation (Vaccines) - engineered to efficiently infect cancer cells preferentially over normal cells, to promote presentation of tumor-associated antigens
  - “Remove the breaks” on T-cell mediated responses (Checkpoint inhibitors)
Immune Checkpoint Inhibitors

• Initial attempts of immunotherapy had marginal success due to the profound dampening of T-cells by inhibitory pathways: CTLA-1, PD-1 and PD-L1

Activation of these pathways is a critical way tumors evade the immune system

• Blocking these pathways (effectively removing the breaks) leads to enhanced T-cell activation and proliferation

• Monoclonal antibodies:
  – CTLA-1: Ipilimumab
  – PD-1: Nivolumab and pembrolizumab
  – PD-L1: Atezolizumab, avelumab and durvalumab

<table>
<thead>
<tr>
<th>Body system/side effect</th>
<th>Nervous system events</th>
<th>Hematologic events</th>
<th>Cardiovascular events</th>
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<tbody>
<tr>
<td>Dermatologic events</td>
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<td>Primary adrenal insufficiency</td>
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<td>Inflammatory arthritis</td>
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<td>Symptomatic nephritis</td>
<td>Nervous system events</td>
<td>Hematologic events</td>
<td>Cardiovascular events</td>
<td>Ocular events</td>
</tr>
</tbody>
</table>
Clinical Case

• 55 yo man, h/o HTN
  – Initial diagnosis 9/2015 with stage IIIc melanoma
  – Rapidly developed skin/in-transit metastases over chest wall, minimal symptoms
  – BRAF V600E mutated
  – Started on ipi/nivo
  – Developed flu-like symptoms 11 days after infusion

Labs

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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<tr>
<td>CKMBRe</td>
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<tr>
<td>MBRat</td>
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<tr>
<td>TRPI</td>
<td>47.23*</td>
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<tr>
<td>CPKTot</td>
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<tr>
<td>BUN</td>
<td>30*</td>
</tr>
<tr>
<td>Creat</td>
<td>1.70*</td>
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<tr>
<td>TBil</td>
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<td>AlkP</td>
<td>183*</td>
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<tr>
<td>AST</td>
<td>1275*</td>
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<tr>
<td>ALT</td>
<td>558*</td>
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</table>
Clinical Case

Patient 1

Days

Ipilimumab and Nivolumab

Troponin I levels

1
10
Admitted
Prednisone started
Patient died
Autopsy

Myocardium, H&E

Myocardium, CD3

Johnson et al, NEJM 2016
These findings are most consistent with:
A. Pericarditis
B. Myocarditis
C. Acute coronary syndrome
D. Arrhythmia
E. Vasculitis
Other cardiac toxicities

- Myocarditis, pericarditis, vasculitis
- No associations with other cardiac issues
Rapid Increase in Reporting of Fatal Immunotherapy Myocarditis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percent (%)</th>
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<tbody>
<tr>
<td>Male gender</td>
<td>66</td>
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<tr>
<td>Cancer</td>
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<tr>
<td>Melanoma</td>
<td>40</td>
</tr>
<tr>
<td>NSCLC</td>
<td>30</td>
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<tr>
<td>Renal</td>
<td>7</td>
</tr>
<tr>
<td>Other*</td>
<td>23</td>
</tr>
</tbody>
</table>

Concomitant medications

- Aspirin: 11%
- Statin: 11%
- Beta blocker: 7%
- ACE/ARB: 12%
- Diuretic medication: 8%

No CV/Diabetes medications: 75%

Regimen

- Anti-PD-1 monotherapy
  - Nivolumab: 43%
  - Pembrolizumab: 15%
- Anti-PD-L1 monotherapy: 3%
- Anti-CTLA-4 (Ipmilimumab) monotherapy: 5%
- Combination anti-PD-1/PD-L1 + anti-CTLA-4: 27%

Timing (median, range): 25 days (5-120)

Concomitant illness

- Myositis/rhabdomyolysis: 25%
- Myasthenia gravis: 10%
- Colitis: 4%
- Severe cutaneous events*: 4%
- Others: 4%

Fatal outcome

- Reporting year
  - 2010 – 2014: 3
  - 2015: 6
  - 2016: 14
  - 2017 (through Dec. 6): 76

Fatality rates:

- Anti-PD-1/PD-L1 plus anti-CTLA-4: 78%
- Anti-PD-1/PD-L1 monotherapy: 42%
  - p=0.004

Toxicity Management

• Cardiac
  – Screening/monitoring not clear
  – Consider troponin, CK, CK-MB weekly for first 3-4 weeks on ipi/nivo
  – Stop if troponin increases
  – High-dose steroids
  – Other agents?
Fatal toxicities

- Rare overall (0.3 – 1.2%)
  - Various, regimen specific causes
  - Tend to occur early

Wang et al, *JAMA Oncology* 2018
What Are CAR T-cells?

Form of cellular immunotherapy using a patient’s own T cells

- Genetically re-engineered T-cells to specifically target a cancer antigen of interest on tumor cells

- Adoptively transferred/infused back into the patient

- Autologous system
  - Ongoing studies for allogeneic CAR-T cells
scFv (single chain variable fragment)
Construction and Advantages with CAR-T

Advantages:
- Virtually every surface antigen can be targeted including non-processed molecules (including carbohydrates and glycolipids)
- No MHC restriction

Disadvantage:
- Toxicities could be derived from when CAR T cells cross-react with an antigen expressed tissue that is similar to the target antigen expressed by the malignancy
General CAR-T Manufacturing/Infusion Process

1. **Collect blood from patient to procure autologous T cells**
2. **Transduce and generate CAR-T cells via gene transfer**
3. **Insert gene for CAR**
4. **Expand autologous CAR-T cell population ex vivo**
5. **Infuse CAR-T cells into patient**

- **CAR-T cell therapy**
- **Chimeric antigen receptor (CAR)**
- **Cytotoxicity**

Ranganathan R, Shea TS. CD30-directed Immunotherapy in Hodgkin and other CD30+ Lymphomas. *Novel Therapeutics for Rare Lymphomas*. Springer, 2019
Summary of CAR T steps

1. Leukapheresis (procure T-cells)
2. Deliver for genetic re-engineering (appx 2 weeks)
3. Consider bridging chemotherapy
4. Administer lymphodepleting chemotherapy (fludarabine and cyclophosphamide)
5. Re-infusion of genetically modified CAR T-cells
6. Supportive care: monitoring for cytokine release syndrome (CRS) and neurotoxicity
B-cell CD19 Directed CAR T Approvals

- Tisagenlecleucel (Kymriah):
  - B cell precursor acute lymphoblastic leukemia in children and young adults (≤25 years old)
  - Diffuse large B cell lymphoma (DLBCL)
    - 4-1BB costimulatory domain
- Axicabtagene ciloleucel (Axi-Cel) (Yescarta):
  - DLBCL
    - CD28 costimulatory domain

Cytokine Release Syndrome

- Early studies uncovered severity of CRS indicated a profound immune response
- Positive feedback leads to progressive elevation in inflammatory cytokines by T-cells
- Marked elevations in C-reactive protein (CRP), interferon γ (IFNγ), tumor necrosis factor α (TNFα), IL-6, IL-10, IL-2, and IL-1β, among other cytokines

<table>
<thead>
<tr>
<th>CTCAE Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>Fever with or without constitutional symptoms</td>
<td>Hypotension responding to fluids; hypoxia responding to &lt;40% O2</td>
<td>Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.

- Rarely: disseminated intravascular coagulation (DIC), capillary leak syndrome, and a hemophagocytic lymphohistiocytosis-like (HLH) syndrome
Cytokine Release Syndrome
Cardiac Toxicities

Axicabtagene ciloleucel

- CRS occurred in 94% of patients
- ≥ Grade 3 in 13% of patients
- Median time to onset: 2 days (range 1-12 days)
- Median duration: 7 days (range 2-58 days)

<table>
<thead>
<tr>
<th>Cardiovascular Adverse Events</th>
<th>Any Grade (%)</th>
<th>≥ Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardiac</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>23</td>
<td>7</td>
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<tr>
<td>Edema</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>57</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>10</td>
<td>1</td>
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</table>
Cytokine Release Syndrome
Cardiac Toxicities

Tisagenlecleucel

- CRS in 79% for B-ALL and 74% for DLBCL
- ≥ Grade 3 in 49% (B-ALL) and 23% (DLBCL)
- Median time to onset: 3 days (range 1-51 days)
- Median duration: 8 days (range 1-36 days)

<table>
<thead>
<tr>
<th>Cardiovascular Adverse Events</th>
<th>Any Grade (%)</th>
<th>≥ Grade 3 (%)</th>
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<tbody>
<tr>
<td>Tachycardia</td>
<td>26</td>
<td>4</td>
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<tr>
<td>Fluid Overload</td>
<td>10</td>
<td>7</td>
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<tr>
<td>Edema</td>
<td>21</td>
<td>1</td>
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<tr>
<td>Dyspnea</td>
<td>16</td>
<td>12</td>
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<tr>
<td>Pulmonary Edema</td>
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<td>4</td>
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<tr>
<td>Hypotension</td>
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<td>22</td>
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<tr>
<td>Hypertension</td>
<td>19</td>
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### Management of CRS

<table>
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<th>CRS Grade (a)</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
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<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).</td>
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<tr>
<td><strong>Grade 2</strong></td>
<td><strong>Administer tocilizumab (c) 8 mg/kg intravenously over 4 hours (not to exceed 800 mg).</strong></td>
<td>Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.</td>
</tr>
<tr>
<td>Symptoms require and respond to moderate intervention.</td>
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<td></td>
</tr>
<tr>
<td>Oxygen requirement less than 40% FiO₂ or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity (b).</td>
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</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td><strong>Per Grade 2</strong></td>
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<tr>
<td>Symptoms require and respond to aggressive intervention.</td>
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<tr>
<td>Oxygen requirement greater than or equal to 40% FiO₂ or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.</td>
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</tr>
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<td><strong>Grade 4</strong></td>
<td><strong>Per Grade 2</strong></td>
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<tr>
<td>Life-threatening symptoms.</td>
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<tr>
<td>Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).</td>
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</table>

**Risk factors for severe CRS:**
- High pre-infusion tumor burden
- Active infections
- Inflammatory processes

Tocilizumab is anti-IL6
A 57 year old male is day 3 after CAR T-cell infusion for DLBCL. Pre-infusion, he had rapidly progressive disease. He develops a fever to 103F, heart rate 130 bpm, hypotension 86/52. An ECG is performed which shows sinus tachycardia. Cultures are collected and he is started on broad spectrum antibiotics. He is given a NS fluid bolus and started on a vasopressor.

Therapy directed towards which of the following should be initiated:
A. Cyclooxygenase-2 (Cox-2)
B. Interleukin-6 (IL-6)
C. Tumor necrosis factor alpha (TNF-α)
D. Major histocompatibility complex (MHC)
Bi-specific T-cell Engagers (BiTEs): Blinatumomab
BiTEs

T Cell

Anti-CD3 Arm

Anti-BCMA Arm

BCMA+ MM Cell

Anti-CD3 Arm

Anti-CD38 Arm

CD38+ myeloma cell
BCMA-BiTE-Based Immunotherapies

### Bispecific Antibodies

**Targets in MM**
- BCMA
- CD38
- SLAMF7
- CD16
- PD-1
- CD3
- CD19
- CD33

**BiTE, bispecific T-cell engager**

**Molecules**
- JNJ-64007957 (BCMA, DuoBody, Phase 1)
- Blinatumomab (CD19, BiTE, Phase 1)
- BI 836909 (BCMA, BiTE, Phase 1)
- AMG 420 (BCMA, BiTE, Phase 1)
- GBR1342-101 (CD38, BiTE, Phase 1)
- PF-06863135 (BCMA, BiTE, Phase 1)
- JNJ-64407564 (BCMA, BiTE, Phase 1)
- FCR4350A (FcRH5, BiTE, Phase 1)
- JNJ-644007957 (BCMA, BiTE, Phase 1)
- CC-93269 (BCMA, BiTE, Phase 1)
Treatment with AMG 420, an Anti-BCMA BiTE, in Relapsed and/or Refractory Multiple Myeloma Patients

Results of a First-in-Human (FIH) Phase 1 Dose Escalation Study

- 35 patients treated
- Efficacy
  - 6 CRs/2 PRs
  - All patients at 400 μg/d dose (3/3) had MRD-CR
- Safety
  - 17 serious AEs
    - Infections
    - CRS

RRMM and progression after ≥2 prior treatment regimens

AMG 420

Single patient cohorts
0.2–1.6 μg/d

3–6 patients cohorts
3.2–800 μg/d

Up to 5, six-week cycles (4 weeks continuous IV infusion, 2 weeks off)

MRD defined as <1 MM cell/10^4 normal cells in BM by flow cytometry

CRS, cytokine release syndrome

You are designing a phase 1 clinical trial against follicular lymphoma. This study will utilize BiTE therapy to recruit T-cells to engage B-cells.

The following antigen should be used for T-cell arm:
A. CD19
B. BCMA
C. CD3
D. CD20
Monoclonal Antibodies

- Mouse challenged with antigen
- Fusion
- Hybridomas
- Culture in HAT Medium
- Select for positive cells
- Harvest monoclonal antibodies

<table>
<thead>
<tr>
<th>Type</th>
<th>Murine (0% human)</th>
<th>Chimeric (65% human)</th>
<th>Humanised (&gt;90% human)</th>
<th>Human (100% human)</th>
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<tbody>
<tr>
<td>Suffix:</td>
<td>-omab</td>
<td>-ximab</td>
<td>-zumab</td>
<td>-umab</td>
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</table>

High Potential for immunogenicity Low
Elotuzumab is anti-SLAMF7 (CS1) and uses NK cells to kill myeloma

- Elotuzumab is a humanized IgG1 monoclonal antibody that recognizes SLAMF7 (CS1)
- SLAMF7 is a protein highly expressed by myeloma and natural killer (NK) cells
- Elotuzumab causes myeloma cell death via a dual mechanism of action
  - Directly activating NK cells
  - ADCC

SLAMF7-Signaling Lymphocyte Activation Molecule Family member 7
ADCC: antibody dependent cell-mediated cytotoxicity

Daratumumab is anti-CD38

IgG1κ human monoclonal antibody against CD38

<table>
<thead>
<tr>
<th>Name</th>
<th>Marketed by</th>
<th>Class</th>
<th>Target</th>
<th>First approved indication</th>
<th>Reported mechanisms of action</th>
<th>Approval year</th>
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<tbody>
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<td>Rituximab (Rituxan)</td>
<td>Biogen Idec/Genentech</td>
<td>Chimeric IgG1</td>
<td>CD20</td>
<td>Non-Hodgkin’s Lymphoma</td>
<td>ADCC, CDC, Induction of Apoptosis</td>
<td>1997</td>
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<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Genentech</td>
<td>Humanized IgG1</td>
<td>HER2</td>
<td>Breast Cancer</td>
<td>Signal Inhibition, ADCC</td>
<td>1998</td>
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<td>Alemtuzumab (Campath)</td>
<td>Sanofi-Aventis</td>
<td>Humanized IgG1</td>
<td>CD52</td>
<td>B cell Chronic Lymphocytic Leukemia</td>
<td>CDC, Induction of Apoptosis</td>
<td>2001</td>
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<td>Ibrutinomab tiuxetan (Zevalin)</td>
<td>Biogen Idec</td>
<td>Murine IgG1</td>
<td>CD20</td>
<td>Non-Hodgkin’s Lymphoma</td>
<td>Radioisotope Delivery ((^{131}I))</td>
<td>2002</td>
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<td>Tositumomab (Bexxar)</td>
<td>GlaxoSmithKline</td>
<td>Murine IgG2a</td>
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<td>Non-Hodgkin’s Lymphoma</td>
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<tr>
<td>Cetuximab (Erbitux)</td>
<td>Bristol-Myers Squibb/Eli Lilly</td>
<td>Chimeric IgG1</td>
<td>EGFR</td>
<td>Squamous Cell Carcinoma of the Head and Neck</td>
<td>Signal Inhibition, ADCC, CDC</td>
<td>2004</td>
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<tr>
<td>Bevacizumab (Avastin)</td>
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<td>Humanized IgG1</td>
<td>VEGF</td>
<td>Colorectal Cancer</td>
<td>Signal Inhibition</td>
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<tr>
<td>Panitumumab (Vectibix)</td>
<td>Amgen</td>
<td>Human IgG2</td>
<td>EGFR</td>
<td>Colorectal Cancer</td>
<td>Signal Inhibition, ADCC</td>
<td>2006</td>
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<td>Ofatumumab (Arzerra)</td>
<td>Genmab/GSK</td>
<td>Human IgG1</td>
<td>CD20</td>
<td>Chronic Lymphocytic Leukemia</td>
<td>ADCC, CDC</td>
<td>2009</td>
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<tr>
<td>Denosumab (Xgeva)</td>
<td>Amgen</td>
<td>Human IgG2</td>
<td>RANKL</td>
<td>Bone Metastases</td>
<td>Signal Inhibition</td>
<td>2010</td>
</tr>
<tr>
<td>Ipilimumab (Yervoy)</td>
<td>Bristol-Myers Squibb</td>
<td>Human IgG1</td>
<td>CTLA-4</td>
<td>Metastatic Melanoma</td>
<td>Signal Inhibition</td>
<td>2011</td>
</tr>
<tr>
<td>Brentuximab vedotin (Adcetris)</td>
<td>Seattle Genetics</td>
<td>Chimeric IgG1</td>
<td>CD30</td>
<td>Hodgkin Lymphoma</td>
<td>ADC</td>
<td>2011</td>
</tr>
<tr>
<td>Pertuzumab (Perjeta)</td>
<td>Genentech</td>
<td>Humanized IgG1</td>
<td>HER2</td>
<td>Breast Cancer</td>
<td>Signal Inhibition, ADCC</td>
<td>2012</td>
</tr>
<tr>
<td>Trastuzumab emtansine (Kadcyla)</td>
<td>Genentech</td>
<td>Humanized IgG1</td>
<td>HER2</td>
<td>Breast Cancer</td>
<td>ADC, Signal Inhibition, ADCC</td>
<td>2013</td>
</tr>
</tbody>
</table>
VEGF signaling plays an important role for maintaining endothelial cell viability and structure.

**Cardio-toxic effects of VEGF inhibition:**
- Hypertension
- LV dysfunction and cardiomyopathy
- Heart failure
- Proteinuria
- Thromboembolism

A newly developed monoclonal antibody called Lenihanomab is developed for prostate adenocarcinoma. This therapy is directed against VEGF.

During initial therapy, monitoring for which of the following is advised:

A. Hypertension
B. Infusion reaction
C. Proteinuria
D. Both A and C
E. All of the above