New Immunotherapies Prior to Stem Cell Transplant

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Disclosures

None
Objectives

• Identify new chemo or immunotherapies that patients may receive prior to hematopoietic cell transplant
• Understand the adverse effects of new chemo or immunotherapies and the impact they may have on stem cell transplant candidacy
• Recognize complications that are associated with new chemo or immunotherapies
Definitions/Terms

ALL – acute lymphoblastic leukemia
AML - acute myeloid leukemia
CR – complete response
HCT- hematopoietic cell transplant
HL- Hodgkin lymphoma
NHL – nonHodgkin lymphoma
SOS - sinusoidal obstruction syndrome
VOD – veno-occlusive disease
What is Immunotherapy?

**American Cancer Society**: Treatment that uses certain parts of a person’s immune system to fight diseases such as cancer

**American Society of Clinical Oncology**: Type of cancer treatment that boosts the body’s natural defenses to fight the cancer. It uses substances made by the body or in a laboratory to improve or restore immune system function.

- Stopping or slowing the growth of cancer cells
- Stopping cancer from spreading to other parts of the body
- Helping the immune system work better at destroying cancer cells

Examples of Immunotherapy

- Monoclonal antibodies
- Non-specific immunotherapies
  - Interferons
  - Interleukins
- Oncolytic virus therapy
- T-cell therapy \textit{(Chimeric antigen receptor CAR T-cell therapy)}
- Cancer vaccines
  - Prevention
  - Treatment

Oncolytic Virus Therapy

- Inject virus into tumor
- Virus makes copies, and kills tumor cells
- Antigens released, triggering immune system to target tumor cells. Sparing healthy cells

• Talimogene laherparepvec (T-VEC) was approved 2015 for patients with melanoma

T-cell Therapy

T-cells removed from patient and sent to a laboratory.

Lab processing to modify cells such that T cells will recognize cancer cells.

Modified T-cells returned to the patient via infusion. T-cells seek out and destroy cancer cells.

- Chimeric Antigen Receptor (CAR) T-cell therapy

Monoclonal Antibodies and Immune Checkpoint Inhibitors

• **Ipilimumab** *(melanoma; lung)*
• **Nivolumab** *(colorectal, head/neck, hepatocellular, hodgkin, melanoma, lung, renal, urothelial)*
• **Pembrolizumab** *(gastric, head/neck, hodgkin, melanoma, lung, urothelial, merkel cell)*
• **Atezolizumab** *(lung, urothelial)*
• **Avelumab** *(merkel, urothelial)*
• **Durvalumab** *(urothelial, lung)*

[www.cancer.net](http://www.cancer.net). ASCO. Accessed January 18, 2018
Disease state specific immunotherapies

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Multiple myeloma
- Hodgkin lymphoma
- Non-Hodgkin lymphoma
Acute Lymphoblastic Leukemia
Acute Lymphoblastic Leukemia

- Represents 0.4% of all new cancer cases in the US
- Most common in children
- Adult 5 year survival rates
  - Less than 45 yr = 74.8%
  - Age 65 yr and older = 47.8%

ALL Standard Therapy

Ph+ ALL (Adolescent and Young Adult-AYA)

- Ages 15-39 years old
- Clinical trial, Chemo + Tyrosine kinase inhibitor (TKI), or TKI + corticosteroids

Ph+ ALL (Adult)

- Stratified to patients less than 65 years without substantial comorbidities OR patients 65 years and older or with substantial comorbidities
- Clinical trial, Chemotherapy + TKI or TKI + corticosteroids (65 yrs or older comorbidities)

Ph- ALL (AYA)

- Clinical trial, Pediatric-inspired regimen, or multi-agent chemotherapy

Ph ALL (Adult)

- Clinical trial, multi-agent chemotherapy, or corticosteroids (for older adults)

Acute Lymphoblastic Leukemia (ALL)

NCCN recommendations for relapsed or refractory B-ALL Ph-negative

- Blinatumomab (category 1)
- Inotuzumab ozogamicin (category 1)
- Cyatarabine-containing regimens
- Alkylator combination regimens
- Augmented hyper-CVAD
- Clofarabine-containing regimens
- MOpAD
- Tisagenlecleucel (patients <26 yo with refractory or ≥ relapses)

Blinatumomab

- Relapsed or refractory B-cell precursor acute lymphoblastic leukemia in adults and children
- Bispecific CD19-directed CD3 T cell engager antibody construct
- Blinatumomab activates endogenous T cells by connecting the CD3 antigen in the T cell receptor complex with the CD19 surface antigen on benign and malignant B cells

Blinatumomab Challenges

• Adverse Effects - Cytokine Release Syndrome
• Continuous infusion over 28 days
  • Patients can be transitioned to outpatient therapy
  • Ambulatory home infusion pump
• Logistics
• Patient selection
Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

- Phase III multi-center trial evaluating blinatumomab or standard-of-care chemotherapy
- Primary endpoint: Overall survival
- Results: Median Overall survival
  - Blinatumomab = 7.7 months
  - Chemotherapy = 4.0 months
- Secondary endpoint: Duration of remission
  - Blinatumomab = 7.3 months
  - Chemotherapy = 4.6 months
- Fourteen percent of patients went on to transplant

Blinatumomab and Cytokine Release Syndrome (CRS)

- Infusion related reactions have occurred and may be clinically indistinguishable from CRS
Cytokine Release Syndrome (CRS)

• Non-antigen specific toxicity that occurs as a result of high-level immune activation
• Manifests when large numbers of lymphocytes and/or myeloid cells become activated and release inflammatory cytokines
• Can be life-threatening and fatal

# Clinical Signs and Symptoms of CRS

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fevers ± Rigors, Malaise, Fatigue, Anorexia, Myalgias, Arthralgias, Nausea, Vomiting, Headache</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, Vomiting, Diarrhea</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea, Hypoxemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, Widened pulse pressure, Hypotension, Increased cardiac output, Potentially diminished cardiac output</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Elevated D-dimer, Hypofibrinogenemia ± Bleeding</td>
</tr>
<tr>
<td>Renal</td>
<td>Azotemia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Transaminitis, Hyperbilirubinemia</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, Mental status changes, Confusion, Delirium, Word finding difficulty or frank aphasia, Hallucinations, Tremor, Altered gait, Seizures</td>
</tr>
</tbody>
</table>

# CRS Grading Assessment and Treatment

| Grade 1: Fever, constitutional symptoms | • Supportive Care  
• Assess for Infection |
|----------------------------------------|---------------------------------------------------------------|
| Grade 2: Hypotension, hypoxia, organ toxicity | • Supportive Care (vigilant monitoring)  
• Older Age or co-morbidities, consider tocilizumab ± corticosteroids |
| Grade 3 or 4 | • Vigilant supportive care  
• Tocilizumab  
• ± Corticosteroids |

Inotuzumab Ozogamicin

- Calicheamicin based antibody targeting CD22
- Approved for use in patients with relapsed or refractory B-cell precursor ALL
- Cytoreduction therapy recommended for patients with circulating lymphoblasts (hydroxyurea, steroids, and/or vincristine)
- Hepatotoxicity, including hepatic VOD/SOS and increased risk of post-hematopoietic stem cell transplant non-relapse mortality
- Incidence ~ 14%

Inotuzumab Therapy Information

• Dosing and Schedules
  • Cycle 1 (21 days)
    • Day 1 Dose = 0.8 mg/m²
    • Day 8 and 15 = 0.5 mg/m²
  • Cycles 2-6 (28 days)
    • Days 1, 8 and 15 = 0.5 mg/m²

• Patients intended to proceed to HCT, the recommended duration of treatment is 2 cycles

• Patients that do not achieve a CR/Cri within 3 cycles should discontinue treatment

Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia

- Phase III multi-center trial, adults with relapsed or refractory acute lymphoblastic leukemia
- Primary endpoints: complete remission and overall survival
- Secondary endpoints: safety measures, duration of remission, progression-free survival, rate of stem-cell transplant, percentage of patients below minimal residual disease
- Total of 326 patients enrolled

Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia

- Total of 279 patients enrolled
- Complete remission
  - Inotuzumab = 80.7%
  - Standard therapy = 29.4% (P < 0.001)
- Overall survival
  - Inotuzumab = 7.7 months
  - Standard therapy = 6.7 months (P = 0.04)
- Patients proceeding to transplant
  - Inotuzumab = 41%
  - Standard therapy = 11% (P < 0.0001)

Tisagenlecleucel

• First FDA-approved CAR-T cell therapy ($475,000). Available at approved treatment centers
• Patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse
• CD19-directed genetically-modified autologous T cell immunotherapy
• Lymphodepleting chemotherapy is commonly given 2-14 days prior to infusion of cells
• Patients are instructed to stay within 2 hours of the location of infusion for at least 4 weeks.

Acute Myeloid Leukemia
Acute Myeloid Leukemia (AML)

- Estimated 1.3% of all new cancer cases
- Estimated 5-year survival = 26.9%
- Most commonly diagnosed between the ages of 65-74 years. Median age of 67 years
- Therapy consists of induction chemotherapy followed by post-remission therapy
- Newer targets for therapy
  - FLT3-mutation
  - IDH1 mutation
  - CD33 antibody

Basic Principles of AML therapy

• Induction therapy for patients less than 60 years
  • Clinical trial, traditional “7+3” (infusional cytarabine + anthracycline), High dose cytarabine, FLAG + Ida, “7+3” + midostaurin (FLT3-mutated AML)

• Induction therapy for patients 60 or older
  • Candidate for intensive therapy
    • Clinical trial, “7+3” ± midostaurin (if FLT3-mutation), Lower intensity therapy (azacitidine, decitabine)
  • Not a candidate for intensive therapy
    • Clinical trial, Low intensity therapy (azacitidine, decitabine) preferred, low-dose cytarabine, or best supportive care

The role of HCT in AML

• Post remission therapy (< 60 years)
  • In patients with intermediate-risk or poor-risk cytogenetics with matched sibling or alternative donor
• Post remission therapy (≥ 60 years)
  • Reduced-intensity HCT
• Relapsed disease
• Induction failure

New therapies in AML

- Liposomal cytarabine:daunorubicin (CPX-351)
- Gemtuzumab ozogamicin
- FLT3 Inhibitors
  - Midostaurin
  - Quizartinib
- IDH1&2 Inhibitors
Liposome-encapsulated daunorubicin and cytarabine

- Approved for use in adults with newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes
- Fixed ratio of daunorubicin:cytarabine
- Given on days 1, 3, and 5 during induction and days 1 and 3 during consolidation
- Improved overall survival in Phase III trial
  - Liposome daunorubicin:cytarabine = 9.6 months
  - Traditional “7+3” chemotherapy = 5.9 months
Midostaurin

- Adults with newly diagnosed acute myeloid leukemia who are FLT3 mutation-positive
- Used in combination with standard cytarabine and daunorubicin
- Oral 25 mg capsule
- Dosing: 50 mg by mouth twice daily with food on Days 8-21 during induction and consolidation chemotherapy

Midostaurin[ Product Package Insert].Novartis.East Hanover, NJ.2017
Midostaurin plus chemotherapy for acute myeloid leukemia with FLT3 mutation

- **RATIFY**- multi-institutional, multi-national, randomized, double-blind, placebo-controlled trial
- Seven hundred, seventeen patients enrolled
- Median overall survival ($P = 0.009$)
  - Midostaurin = 74 months
  - Placebo = 25.6 months
- The benefit of midostaurin was observed among patients who underwent transplantation during the first remission but not among those who underwent transplantation at a later time

Enasidenib

- Adults with relapsed or refractory AML with isocitrate dehydrogenase-2 (IDH2) mutation
- Dose = 100 mg po daily
- Differentiation syndrome (14% incidence)
  - Hypoxia, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain, peripheral edema, fever, lymphadenopathy, bone pain, and hepatic, renal or multi-organ dysfunction
  - Initiate corticosteroid and hemodynamic monitoring

Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia

- Primary objective was to determine the safety and MTD of enasidenib
- Safety: 82% of patients experienced a treatment-emergent adverse event (TEAE). Hyperbilirubinemia, nausea, differentiation syndrome
- Efficacy
  - Overall response rate = 40.3%
  - Median time to first response = 1.9 months
  - Median overall survival among patients with relapsed/refractory AML = 9.3 months

Gemtuzumab ozogamicin

- Originally FDA approved in 2000
- Removed from the market in 2010
- European research incorporated smaller, fractionated doses and demonstrated improved overall survival
- FDA approval September 2017
  - Newly diagnosed CD33-positive AML in adults
  - Relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older

Gemtuzumab ozogamicin- VOD risk

• Historically, concern regarding increased risk of VOD in patients undergoing HCT within 3 months of receiving gemtuzumab ozogamicin
  • Prior dosing 9mg/m2 IV on days 1 and 15
• Fractionated dose schedules used in European studies appear to have lowered risk, but remains to be shown in larger randomized phase III trials
  • Combination: 3 mg/m2 (max 4.5mg) on Days 1,4 and 7
  • Single agent: 6 mg/m2 Day1 and 3mg/m2 Day8
  • Single agent: 3 mg/m2 on Days 1,4, and 7

Multiple Myeloma
Multiple Myeloma

• Overview: Blood cancer that affects the plasma cells, most frequently diagnosed between the ages of 65-74
• Estimated 1.8% of new cancer cases
• Estimated 5-year survival = 49.6%
• Multiple new therapies approved in late 2015 and 2016
• HCT still considered first line in eligible patients
• Newer therapies usually incorporated after recurrent disease and prior to subsequent HCT

Classes of therapy

- Chemotherapy
- Steroids
- Immunomodulatory agents
  - Lenalidomide, Pomalidomide, Thalidomide
- Proteasome inhibitors
  - Bortezomib, Carfilzomib, Ixazomib
- Monoclonal antibody
  - Daratumumab, Elotumumab
- Histone deacetylase inhibitor (HDAC inhibitor)
  - Panobinostat
Primary Therapy

Autologous transplant (category 1)

Stable disease ➔ Maintenance

Progressive disease

- Therapy for previously treated myeloma
- Clinical trial +/- additional autologous transplant
- Allogeneic transplant
NCCN recommendations for treatment in transplant eligible patients

Preferred regimens
- Bortezomib/lenalidomide/dexamethasone
- Bortezomib/cyclophosphamid/dexamethasone

Other recommended regimens
- Bortezomib/doxorubicin/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone

Useful in certain circumstances
- Bortezomib/dexamethasone
- Bortezomib/thalidomide/dexamethasone
- Lenalidomide/dexamethasone
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib

NCCN therapy recommendations for previously treated patients

Preferred Regimens

- Repeat primary induction therapy *if relapse at > 6 months*
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib (twice weekly)/dexamethasone *(Cat 1)*
- Carfilzomib/lenalidomide/dexamethasone *(Cat 1)*
- Daratumumab/bortezomib/dexamethasone *(Cat 1)*
- Daratumumab/lenalidomide/dexamethasone *(Cat 1)*
- Elotuzumab/lenalidomide/dexamethasone *(Cat 1)*
- Ixazomib/lenalidomide/dexamethasone *(Cat 1)*

Primary Therapy

Autologous transplant (category 1)

Stable disease → Maintenance

Progressive disease
- Therapy for previously treated myeloma
- Clinical trial +/- additional autologous transplant
- Allogeneic transplant
Elotuzumab

- Signaling Lymphocytic Activation Molecule Family member 7 protein (SLAMF7)-directed immunostimulatory antibody
- Activates Natural Killer (NK) cells and identifies myeloma cells so they are recognized by NK cells
- Indication: Combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies

Elotuzumab Dosing Schedule

Recommended dosing 10 mg/kg every week for the first two cycles and every 2 weeks thereafter.

Premedications

- Dexamethasone
- H₁ blocker: diphenhydramine or equivalent
- H₂ blocker: ranitidine or equivalent
- Acetaminophen

Daratumumab

CD-38 directed cytolytic antibody

Indications

- Combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, in patients who have received at least one prior therapy
- Combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)
- Monotherapy when patients have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and immunomodulatory agent

Daratumumab dosing schedules
16 mg/kg actual body weight

Monotherapy
Weeks 1 to 8
- Weekly, total of 8
Weeks 9 to 24
- Every 2 weeks, total of 8
Week 25 onwards
- Every 4 weeks until disease progression

Combination
Weeks 1-9
- Weekly, total of 9
Weeks 10-24
- Every 3 weeks, total of 5
Weeks 25 onward
- Every 4 weeks until disease progression

Daratumumab Infusion-Related Reactions

Pre-infusion medications (1-3 hours prior)

- Corticosteroids (depends on mono/combo therapy)
- Antipyretics (acetaminophen)
- Antihistamine (diphenhydramine)

Post-infusion medications (reduce risk of delayed reactions)

- Additional corticosteroids

Additional Considerations

- Patients with chronic obstructive pulmonary disease: consider post-infusion short and long acting bronchodilators and inhaled corticosteroids

Daratumumab Interferences

Blood banking considerations

- Interferences with cross-matching and red blood cell antibody screening. Results in a positive indirect antiglobulin test (Indirect Coombs). This can persist for up to 6 months after the last dose

- Patients should be typed and screened prior to starting treatment. Good communication with blood bank

Determining disease response (human IgG kappa monoclonal antibody)

- Can be detected on both serum protein electrophoresis (SPE) and immunofixation (IFE) assays.

- IgG kappa myeloma protein

Panobinostat

- Oral histone deacetylase inhibitor, works at the DNA level. Needs to be given in combination
- Approved for use in combination with bortezomib and dexamethasone for patients who received 2 prior lines of therapy that included bortezomib and an immunomodulatory age.
- PANORAMA-1 trial: Randomized placebo-controlled phase III study
- PANORAMA-2 trial: Phase II single-arm, multicenter trial

Ixazomib

- First oral proteosome inhibitor
- Advantages include oral route and weekly administration
- Approved for use in combination with lenalidomide and dexamethasone in patients who have received at least 1 prior treatment
- Progression free survival advantage
  - Ixazomib = 20.6 months
  - Placebo + Len + Dex = 14.7 months

Carfilzomib

- Second generation proteasome inhibitor
- Approved as single use, combination with dexamethasone or dexamethasone and lenalidomide
- Most commonly used in progression after first line therapy, but some evidence supporting initial therapy
- Less neurotoxicity
- Given intravenously, commonly twice weekly on 3 of 4 week schedule

Hodgkin Lymphoma
Hodgkin Lymphoma

- Represents 0.5% of new cancer cases
- Survival rate @ 5 years = 86.4%
- Role of HCT in adults
  - CR1 (PET positive)-Auto
  - Primary refractory, sensitive-Allo/Auto
  - Primary refractory, resistant-Allo
  - First relapse, sensitive – Allo/Auto
  - First relapse, resistant – Allo
  - Second or greater relapse – Allo/Auto
  - Relapse after auto - Allo

Anti-Program Death 1 (PD-1)

- PD-1 signaling regulates the immune response by decreasing T-cell activation and suppressing T-cell proliferation and cytokine production
  - Nivolumab
  - Pembrolizumab
- Approved for use in solid tumors such as colorectal, head and neck, hepatocellular, melanoma, lung cancers

PD-1 Inhibition in Hodgkin Lymphoma

- Patients with classical HL have PD-1 ligand overexpression, most commonly on Reed-Sternberg cells
- Epstein-Barr virus also leads to PD-L1 up-regulation
- By engaging with PD-1, PD-L1 delivers a potent immune-suppressive signal characterized by decreased T-cell proliferation, modulation of cytokine release, and increased susceptibility to apoptosis

Checkpoint Inhibitors in Hodgkin Disease

- FDA Approved Indications
  - Nivolumab in patients with classic HL that has relapsed or progressed after autologous transplant or 3 or more lines of systemic therapy that include autologous transplant
  - Pembrolizumab for adult and pediatric patients with refractory classic HL or those who have relapsed after 3 or more prior therapies

Recommendations for Checkpoint Inhibitors

- Recommended in patients with refractory classic HL, who are transplant-ineligible based on comorbidity or failure of first salvage chemotherapy
- Any patient who has relapsed after autologous transplant ± brentuximab
- Post-allogeneic transplant patients can receive either agent, but caution is advised due to increased risk of GVHD and other immunological complications
- Only pembrolizumab has been studied in pediatric patients at this time

Adverse Events of Anti-PD-1 Therapies

<table>
<thead>
<tr>
<th>Common Grade 1 or 2</th>
<th>Grade 3 or 4</th>
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<tbody>
<tr>
<td>Pyrexia (11-14%)</td>
<td>Neutropenia (1-5%)</td>
</tr>
<tr>
<td>Hypothyroidism (9-12%)</td>
<td>Increased amylase/lipase (1-8%)</td>
</tr>
<tr>
<td>Diarrhea (7-21%)</td>
<td>Increased AST/ALT (1-2%)</td>
</tr>
<tr>
<td>Rash (6-22%)</td>
<td>Diarrhea (1%)</td>
</tr>
<tr>
<td>Fatigue (7-29%)</td>
<td>Dyspnea (1%)</td>
</tr>
<tr>
<td>Infusion reactions (9-20%)</td>
<td></td>
</tr>
<tr>
<td>Arthralgias (14%)</td>
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- Anti-PD-1 antibodies are long-lived, with half-lives up to 1 month and long-term immunomodulatory effects of unknown duration.

Nivolumab

- Dosing = 3 mg/kg IV every 2 weeks
- Phase I trial (23 patients)
  - Objective response = 87%
  - Complete response = 17%
- Phase II trial – multi-center (80 patients)
  - Objective response = 66.3%
  - Complete response = 8.8%

Pembrolizumab

- Dosing = 2 mg/kg up to 200 mg every 3 weeks
- Phase II trial (KEYNOTE-087)
  - Total of 210 patients
  - Overall response rate = 69 %
  - Complete response rate = 22%
  - Median exposure to pembrolizumab = 8.3 months

Pembrolizumab[product information]. Whitehouse Station, NJ. 08889. 2017
Non-Hodgkin Lymphoma
Non-Hodgkin Lymphoma

- Represents an estimated 4.3% of all new cancers in 2017
- Patients surviving 5 years = 71%
- Role of HCT
  - Diffuse large B cell
  - Follicular
  - Mantle cell
  - T-cell and Cutaneous T-cell
  - Burkitt’s

Common Non-Hodgkin Lymphoma Regimens

- Bendamustine + rituximab
- R-CHOP
- Bendamustine + obinutuzumab
- CVP
- HyperCVAD ± rituximab
- RDHAP
- Dose-adjusted R-EPOCH
- ESHAP ± Rituxan
- GDP
- GemOx
- ICE
- MINE

Acalabrutinib

- Bruton tyrosine kinase (BTK) inhibitor. BTK plays a key role in B-cell receptor signaling
- Mantle-cell lymphoma, who have received at least one prior therapy
- Dose = 100 mg every 12 hours until disease progression or unacceptable toxicity
- Phase II trial, 124 patients, evaluated overall response
  - Overall response = 81% @ median of 15.2 months
  - Complete response = 40%

Copanlisib

- PI3K inhibitor: Plays a significant role in B-cell receptor signaling
- Relapsed follicular lymphoma who have received at least two prior systemic therapies
- Accelerated approval was granted based on Phase II trial demonstrating overall response rate (59%)
  - Complete response = 14%
  - Partial response = 44%
- Intravenous 60 mg infusion given on Days 1, 8, and 15 of a 28-day cycle (3 weeks on and 1 week off)

Copanlisib Monitoring

- **Infections** - Serious, including fatal infections occurred in 19% of patients. Consider PJP prophylaxis.
- **Hyperglycemia** – Grade 3 or 4 (glucose 250 mg/dL or greater) occurred in 41%. Blood glucose level peak 5 to 8 hours post-infusion.
- **Hypertension** – Can be infusion related, Grade 3 occurred in 26% of patients. Patients should have adequate BP control prior to starting therapy.
- **Non-infectious pneumonitis** – Occurred in 5% of patients. Corticosteroids and withhold, reduce dose or discontinue therapy.

Axicabtagene Ciloleucel CAR T-cell Therapy in Refractory Large B-Cell Lymphoma

- Multi-center phase II trial, 111 patients
- Primary endpoint: rate of objective response
- Patients received conditioning chemotherapy consisting of fludarabine 30 mg/m2/dose and cyclophosphamide 500 mg/m2/dose on Days -5, -4, and -3
- Objective response rate = 82% (Complete response – 52%)
- Median time to response = 1 month
- Median duration of response = 8.1 months
