NEW DRUG UPDATE

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Faculty Disclosures

I have no relevant financial interests, arrangements or affiliations with companies or other organizations whose products or services are discussed in this session.

Objectives

- Identify new drug approvals in hematology/oncology in the past year
- Discuss mechanisms of action, dosing, and major toxicities of these agents
- Review relevant clinical trial data for newly approved agents
- Understand the role in therapy of newly approved agents

New Drug Approvals 2013-2014

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Approval Date</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab</td>
<td>Cyramza</td>
<td>4/21/2014</td>
<td>Eli Lilly &amp; Company</td>
<td>Gastric or gastroesophageal junction adenocarcinoma</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Gilotrif</td>
<td>7/12/2013</td>
<td>Boehringer Ingelheim, Inc.</td>
<td>EGFR-mutated NSCLC</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Zykadia</td>
<td>4/29/2014</td>
<td>Novartis</td>
<td>ALK+ NSCLC</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Imbruvica</td>
<td>11/13/2013</td>
<td>Pharmacycics, Inc.</td>
<td>Mantle Cell Lymphoma Chronic Lymphocytic Leukemia</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>Gazyva</td>
<td>11/1/2013</td>
<td>Genentech, Inc.</td>
<td>Chronic Lymphocytic Leukemia</td>
</tr>
<tr>
<td>Belinostat</td>
<td>Beleodaq</td>
<td>7/3/2013</td>
<td>Spectrum Pharmaceuticals</td>
<td>Peripheral T-cell Lymphoma</td>
</tr>
<tr>
<td>Siltuximab</td>
<td>Sylvant</td>
<td>4/23/2014</td>
<td>Janssen Biotech, Inc.</td>
<td>Multicentric Castleman’s Disease</td>
</tr>
</tbody>
</table>

Ramucirumab

- FDA Approval: April 21, 2014
  - Single agent for advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma
  - Disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy.

- Human IgG1 Antiangiogenic Monoclonal Antibody
Ramucirumab: REGARD Trial

Ramucirumab monotherapy for previously treated advanced gastric or GEJ adenocarcinoma

- **Design:** International, randomized, multicenter, placebo-controlled, phase III trial
- **Objective:** To assess whether ramucirumab prolonged survival in patients with advanced gastric cancer

REGARD Trial Results: Overall Survival

- **Median OS:**
  - Ramucirumab: 5.2 months
  - Placebo: 3.8 months

REGARD Trial Results: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td><strong>Bleeding/hemorrhage</strong></td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td><strong>Arterial thromboembolism</strong></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Venous thromboembolism</strong></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Gastrointestinal perforation</strong></td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Fistula formation</strong></td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Infusion-related reaction</strong></td>
<td>&lt;1</td>
<td>0</td>
</tr>
</tbody>
</table>

Ramucirumab Dosing and Pharmacokinetics

- **Dosing:** 8 mg/kg IV over 60 minutes every 2 weeks until disease progression or unacceptable toxicity

- **Preparation and Administration:**
  - Preparation: Do not dilute with dextrose containing solutions
  - Premedication: diphenhydramine ± acetaminophen and dexamethasone (if previous Grade 1 or 2 infusion reaction)

- **Pharmacokinetics**
  - Receptor-mediated clearance
  - Half-life: 123-318 hours
**Ramucirumab Role in Therapy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Treatment</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang et al. JCO 2012</td>
<td>N = 202</td>
<td>Docetaxel or Irinotecan + BSC vs. Placebo + BSC</td>
<td>5.3 mo vs. 3.8 mo HR: 0.667; p = 0.007</td>
</tr>
<tr>
<td>Ford et al. Lancet Oncol 2014 (CONCUR-02)</td>
<td>N = 168</td>
<td>Docetaxel + ASC vs. Placebo + ASC</td>
<td>5.2 mo vs. 3.6 mo HR: 0.67; p = 0.01</td>
</tr>
<tr>
<td>Fuchs et al. Lancet Oncol 2014 (REGARD)</td>
<td>N = 355</td>
<td>Ramucirumab + BSC vs. Placebo + BSC</td>
<td>5.2 mo vs. 3.8 mo HR: 0.67; p = 0.047</td>
</tr>
<tr>
<td>Wilke et al. ASCO GI 2014 (RAINFOREST)</td>
<td>N = 655</td>
<td>Ramucirumab vs Placebo + Paclitaxel</td>
<td>6.93 mo vs. 7.36 mo HR: 0.807; p = 0.016</td>
</tr>
</tbody>
</table>

BSC = Best Supportive Care; ASC = Active Symptom Control

**Afinatinb**

- **FDA Approval:** July 12, 2013
  - First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 substitution mutations
  - EGFR PCR kit approved for detection of these mutations

- **Tyrosine kinase inhibitor of EGFR**

**Afinatinb Mechanism of Action**

**Afinatinb Dosing and Pharmacokinetics**

- **Dosing:** 40 mg PO daily until disease progression or intolerance
  - **Absorption**
    - Steady state achieved within 8 days
    - High-fat meal: decreased Cmax by 50% and AUC by 30%
  - **Metabolism**
    - Minimal enzymatic metabolism
    - Pgp inhibitors: increased exposure by 48%
    - Pgp inducers: decreased exposure by 34%
  - **Elimination**
    - Half-life: 37 hours
    - 85% excreted via feces; 4% in urine
    - 88% recovered dose was parent compound

**Afinatinb: LUX-Lung 3 Trial**

Afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations


- **Design:** Multinational, randomized, open-label phase III trial
- **Objective:** To assess if afatinib improved PFS over chemotherapy in EGFR-mutated NSCLC

**Afatinib: LUX-Lung 3 Trial**

- **Randomization**
  - N = 345
    - Activating EGFR mutation
    - Treatment-naïve advanced NSCLC (adenocarcinoma)
    - ECOG 0-1
- **Treatment (PFS)**
  - N = 230
    - Afatinib 40 mg PO daily
  - N = 115
    - Cisplatin 75 mg/m² + Pemetrexed 500 mg/m² once every 21 days x 6 cycles
Afatinib Dose Modifications

- **Interrupt therapy:**
  - Any Grade 3+ adverse reaction
  - Diarrhea: Grade 2+ persisting for 2+ days while on treatment
  - Cutaneous reactions: Grade 2+ lasting > 7 days or intolerable
  - Renal dysfunction: Grade 2+

- **Resume with 10 mg/day dose reduction:**
  - Resolution of adverse reaction
  - Return to baseline
  - Improvement of adverse reaction to Grade 1

Afatinib Role in Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
</table>
| Miller et al. Lancer Oncol. 2012 (LUX-Lung 1) N = 585 | Afatinib + RSC vs. Placebo + RSC | OS: 10.8 mo vs. 12.0 mo  
HR: 1.08; p = 0.74  
PFS: 3.3 mo vs. 2.1 mo  
HR 0.38; p = 0.0001 |
| Katakami et al. J Clin Oncol 2013 (LUX-Lung 4) N = 62 (Asian) | Afatinib (single-arm) | ORR: 8.2% (all PRs)  
Stable Disease: 57.4%  
PFS 4.4 mo |
| Sequist et al. J Clin Oncol 2013 (LUX-Lung 3) N = 345 | Afatinib vs. cisplatin + pemetrexed | PFS: 11.1 mo vs. 6.9 mo  
HR: 0.38; p < 0.001 |
| Wu et al. Lancer Oncol 2014 (LUX-Lung 6) N = 364 (Asian) | Afatinib vs. cisplatin + gemcitabine | PFS: 11.6 mo vs. 5.6 mo  
HR: 0.28; p < 0.0001 |

Ceritinib

- **FDA Approval:** April 29, 2014
  - Accelerated approval for treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib

- **Anaplastic Lymphoma Kinase (ALK) Inhibitor**
Ceritinib Dosing and Pharmacokinetics

- **Dosing:** 750 mg PO daily
- **Time to C<sub>ss</sub>:** 15 days
- **Food-effect**
  - 600 mg + food > 750 mg fasting
  - Take on EMPTY STOMACH!
- **pH-dependent solubility**
  - Caution gastric acid reducing agents

**Pharmacokinetics**

- **Metabolism:** extensively hepatic via CYP3A
  - Strong inhibitor: 3-fold increase in AUC; 22% increase in Cmax
  - Strong inducer: 70% decrease in AUC; 44% decrease in Cmax
  - Substrate of P-gp; no inhibitory activity
- **Elimination:**
  - Half-life: 41 hours
  - 92% recovered in feces (68% as parent compound)
  - 1.3% recovered in urine

Ceritinib: ASCEND-1 Trial

Ceritinib in advanced ALK-rearranged NSCLC
Kim D et al. *J Clin Oncol*. 2014;32:5s (suppl; abst 8003)

- **Design:** Multinational, single-arm, open-label dose-escalation study with expansion phase
- **Objective:** to determine maximum tolerated dose (MTD) and antitumor activity of ceritinib

ASCEND-1 Trial Results: Response

- **MTD = 750 mg PO daily**
- **N = 255 patients treated at 750 mg PO daily**
  - 163 (64%) pts with previous ALK-inhibitor therapy
  - Median follow-up: 4.5 months

<table>
<thead>
<tr>
<th></th>
<th>ALK inhibitor pretreated N = 121</th>
<th>ALK inhibitor naive N = 79</th>
<th>All N = 180</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>55.4</td>
<td>69.5</td>
<td>60.0</td>
</tr>
<tr>
<td>DOR (months)</td>
<td>7.4</td>
<td>NR</td>
<td>9.7</td>
</tr>
<tr>
<td>Time to 1&lt;sup&gt;st&lt;/sup&gt; response (weeks)</td>
<td>6.1</td>
<td>6.1</td>
<td>6.1</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>6.9</td>
<td>NR</td>
<td>7.0</td>
</tr>
<tr>
<td>NR = Not Reached</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASCEND-1 Trial Results: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>86</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>80</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td>ALT increased</td>
<td>80</td>
<td>27</td>
</tr>
<tr>
<td>AST increased</td>
<td>75</td>
<td>13</td>
</tr>
<tr>
<td>T. Bili increased</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>49</td>
<td>13</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>36</td>
<td>7</td>
</tr>
</tbody>
</table>

Other Warnings and Precautions:
- QTc prolongation: 4%
- Bradycardia: 3%
- Vision disorders: 9%
- Interstitial Lung Disease/Pneumonitis: 4%
- Rash: 16%
- Neuropathy: 17%

Ceritinib Dosing Adjustments

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/AST &gt;3 x ULN + T. bili &lt; 2 x ULN</td>
<td>Hold until back to baseline or ≤ 3 x ULN; resume with 150 mg reduction</td>
</tr>
<tr>
<td>ALT/AST &gt;3 x ULN + T. bili ≥ 2 x ULN</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>QTc interval &gt;500 msec x 2</td>
<td>Hold until QTc back to baseline or &lt;481 msec; resume with 150-mg reduction</td>
</tr>
<tr>
<td>Symptomatic Bradycardia</td>
<td>Hold until asymptomatic or HR of &lt;60 bpm; adjust concomitant medications</td>
</tr>
<tr>
<td>Severe/Intolerable N/V/D</td>
<td>Hold until improved; resume with 150-mg reduction</td>
</tr>
<tr>
<td>Hyperglycemia &gt;250 mg/dL</td>
<td>Hold until controlled; resume with 150-mg reduction</td>
</tr>
</tbody>
</table>

Ceritinib Role in Therapy

- Ceritinib vs. standard chemotherapy (pemetrexed or docetaxel) in ALK-positive advanced NSCLC who have been treated previously with chemotherapy (platinum doublet) and crizotinib (NCT01828112)
- Ceritinib vs. standard chemotherapy in previously untreated patients with ALK-rearranged, Stage IIIB or IV NSCLC (NCT01828099)

www.clinicaltrials.gov

Audience Response Question

Which of the following is true about ceritinib?

A. Ceritinib has less potent inhibition of ALK than crizotinib
B. Ceritinib should be taken on an empty stomach
C. Ceritinib exhibits no response in patients previously treated with an ALK-inhibitor
D. Ceritinib should be taken with a high-fat meal

Ibrutinib

- FDA Approval:
  - November 13, 2013: Granted accelerated approval for mantle cell lymphoma (MCL) patients who have received at least one prior therapy
  - February 12, 2014: Granted accelerated approval for chronic lymphocytic leukemia (CLL) patients who have received at least one prior therapy

- Bruton’s Tyrosine Kinase (BTK) Inhibitor

Ibrutinib Mechanism of Action

Ibrutinib Dosing and Pharmacokinetics

- Dosing:
  - Mantle Cell Lymphoma: 560 mg PO daily
  - Chronic Lymphocytic Leukemia: 420 mg PO daily

- Food Effect: Increase AUC 2-fold

- Metabolism: Extensively hepatic via CYP3A, CYP2D6
  - Strong CYP3A inhibitor: increases AUC 24-fold; Cmax 29-fold
  - Moderate CYP3A inhibitor: increases AUC 6 to 9-fold
  - Strong CYP3A inducer: 10-fold decrease in concentrations
  - Active metabolite: 15x less inhibitory activity than ibrutinib

- Elimination:
  - Half-life: 4-6 hours
  - 80% excreted in feces; <10% in urine

**Ibrutinib in Mantle Cell Lymphoma**

Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma


- **Design:** International, open-label, phase 2, single arm study

- **Objective:** To determine the ORR of ibrutinib in relapse/refractory MCL.

**Ibrutinib in MCL: Response**

<table>
<thead>
<tr>
<th></th>
<th>No Bortezomib (N = 65)</th>
<th>Prior Bortezomib (N = 49)</th>
<th>All (N = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (%)</strong></td>
<td>68</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td><strong>CR (%)</strong></td>
<td>19</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td><strong>PR (%)</strong></td>
<td>49</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td><strong>DOR (months)</strong></td>
<td>15.8</td>
<td>NR</td>
<td>17.5</td>
</tr>
<tr>
<td><strong>FFS (months)</strong></td>
<td>7.4</td>
<td>16.6</td>
<td>13.9</td>
</tr>
</tbody>
</table>

NR = not reached

**Ibrutinib in CLL**

Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia


- **Design:** Multicenter, single-arm, phase 1b-2 study

- **Objective:** To assess safety, efficacy, pharmacokinetics and pharmacodynamics of ibrutinib in relapsed CLL

**Ibrutinib in CLL**

N = 85 previously treated CLL patients

420 mg (n = 51) vs. 840 mg (n = 35)

PK: Similar PK profile
PD: Full BTK occupancy at both doses
Similar Response Rates (ORR: 71%)

**Ibrutinib Dose Adjustments**

- **Interrupt therapy for:**
  - ≥ Grade 3 non-hematological adverse event
  - ≥ Grade 3 or greater neutropenia with fever/infection
  - Grade 4 hematologic toxicity

- **Resume therapy once toxicity has resolved to Grade 1 or baseline**

**Ibrutinib Adverse Events**

<table>
<thead>
<tr>
<th>All Adverse Events (≥ 20%)</th>
<th>≥ Grade 3 (≥5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Skin Infections</td>
</tr>
<tr>
<td>Anemia</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Abdominal Pain</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Bleeding events</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td></td>
</tr>
<tr>
<td>Bruising</td>
<td></td>
</tr>
</tbody>
</table>

**Ibrutinib**

Ibrutinib Role in Therapy

- RESONATE: Ibrutinib vs. Ofatumumab in Patients with Relapsed or Refractory CLL
  - PFS: HR 0.215; p <0.001; OS: HR 0.434; p = 0.0049
- Ibrutinib Versus Ibrutinib + Rituximab (i vs iR) in Patients With Relapsed Chronic Lymphocytic Leukemia (CLL)
- Rituximab and Bendamustine Hydrochloride, Rituximab and Ibrutinib, or Ibrutinib Alone in Treating Older Patients With Previously Untreated Chronic Lymphocytic Leukemia
- RESONATE-2: Ibrutinib vs. Chlorambucil in Patients 65 Years or Older with Treatment-naïve CLL or SLL

Audience Response Question

Which of the following is NOT true about ibritinib?

A. Ibrutinib inhibits Bruton’s tyrosine kinase
B. CYP3A inhibitors should be cautioned with ibritinib
C. Ibrutinib is approved for both MCL and CLL in patients who have received at least one prior therapy
D. Ibrutinib is approved at a dose of 560 mg PO daily for MCL and CLL

Obinutuzumab

- FDA Approval: November 1, 2013
  - In combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia
- Type II anti-CD20 humanized monoclonal antibody

Obinutuzumab Mechanism of Action

Obinutuzumab Dosing and Administration

- Dosing
  - 28-day cycles x 6 cycles
  - Premedicate: glucocorticoid, acetaminophen, anti-histamine

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 8</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>900 mg</td>
<td>1000 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg/hr</td>
<td>Initial: 50 mg/hr</td>
<td>Initial: 100 mg/hr</td>
<td>Max: 400 mg/hr</td>
<td></td>
</tr>
</tbody>
</table>

Cycles 2-6

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day 1</th>
<th>1000 mg</th>
</tr>
</thead>
</table>

Obinutuzumab for CLL

Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions


- Design: Randomized, open-label, multicenter phase III trial
- Objective: To evaluate if obinutuzumab provides a PFS benefit in previously untreated CLL
**Obinutuzumab for CLL**

- Patients: 781 Patients
- Previously untreated CLL
- Cumulative Illness Rating Scale (CIRS) Score > 6
- CrCl 30-69 ml/min

**Randomization**

- N = 118 Chlorambucil 0.5 mg/kg PO days 1 & 15 of 28 day cycle
- N = 238 Obinutuzumab + Chlorambucil
- N = 233 Rituximab 775 mg/m2 C1D1; 500 mg/m2 C2-6D1 + chlorambucil

**Chlorambucil**


**Obinutuzumab in CLL: PFS**

- Stratified hazard ratio for progression or death with G-Cb, 0.18 (95% CI, 0.11–0.34) \( P = 0.001 \)

**Obinutuzumab in CLL: Adverse Events**

<table>
<thead>
<tr>
<th>Obinutuzumab + Chlorambucil</th>
<th>Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>69</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>40</td>
</tr>
<tr>
<td>Anemia</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>7</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
</tr>
</tbody>
</table>

**Obinutuzumab Infusion-Related Reactions**

**Premedication Recommendations**

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Day 1-2</th>
<th>All</th>
<th>Dexamethasone 20 mg IV</th>
<th>Methylprednisolone 80 mg IV</th>
<th>1 hour prior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>Day 8, 15</td>
<td>All</td>
<td>APAP 650-1000 mg</td>
<td>30 mins prior</td>
<td></td>
</tr>
<tr>
<td>Cycles 2-6</td>
<td>Day 1</td>
<td>&gt; Grade 1 IRR</td>
<td>Diphenhydramine 50 mg</td>
<td>30 mins prior</td>
<td></td>
</tr>
<tr>
<td>Cycles 2-6</td>
<td>Day 1</td>
<td>Grade 3 IRR or lymphocyte count &gt; 25 × 10^9/L</td>
<td>Dexamethasone 20 mg IV</td>
<td>Methylprednisolone 80 mg IV</td>
<td>1 hour prior</td>
</tr>
</tbody>
</table>

**Obinutuzumab Boxed Warnings**

- Hepatitis B Virus (HBV) reactivation
  - Fulminant hepatitis, hepatic failure, death
  - Screen for HBV before initiation of therapy
- Progressive Multifocal Leukoencephalopathy (PML)
  - Potentially lethal
Obinutuzumab Role in Therapy

- Phase IIIb study evaluating the safety of obinutuzumab alone or in combination with chemotherapy in patients with previously untreated or relapsed/refractory CLL.
- A study evaluating the efficacy and safety of obinutuzumab and bendamustine treatment in patients with refractory or relapsed CLL.

www.clinicaltrial.gov

Audience Response Question

Which of the following is not recommended for obinutuzumab infusion-related reactions?

A. Acetaminophen 650 mg PO
B. Diphenhydramine 50 mg PO
C. Hydrocortisone 100 mg IV
D. Dexamethasone 20 mg IV

Belinostat

- FDA Approval: July 3, 2014
  - Accelerated approval for treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)
- Histone deacetylase (HDAC) inhibitor

Belinostat Mechanism of Action

Belinostat Dosing and Pharmacokinetics

- Dosing: 1,000 mg/m² IV over 30 minutes on days 1-5 of 21-day cycle.
- Pharmacokinetics
  - Primary metabolism: UGT1A1
  - Secondary metabolism: CYP2A6, CYP2C9, CYP3A4
  - Inhibitory activity: CYP2C8, CYP2C9
  - Urinary excretion of metabolites

Belinostat: BELIEF Trial

Belinostat in relapsed or refractory peripheral T-cell lymphoma.

O’Connor et al. J Clin Oncol. 2013 (suppl; abstr 8507)

- Design: Multicenter phase II single-arm trial
- Objective: To assess overall response rate of belinostat in relapsed/refractory PTCL
**Belinostat: BELIEF Trial**

- N = 129
- Median number of prior therapies: 2
- No prior HDAC Inhibitor therapy

<table>
<thead>
<tr>
<th>Belinostat (n = 129)</th>
<th>Adverse Events (≥Grade 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR 26%</td>
<td>Thrombocytopenia (7 %)</td>
</tr>
<tr>
<td>CR 10%</td>
<td>Neutropenia (6 %)</td>
</tr>
<tr>
<td>PR 16%</td>
<td>Anemia (11 %)</td>
</tr>
<tr>
<td>DOR (months) 8.3</td>
<td>Dyspnea (6 %)</td>
</tr>
<tr>
<td></td>
<td>Fatigue (5 %)</td>
</tr>
</tbody>
</table>

**Non-Malignant Hematology**

**NEW DRUG UPDATE**

**Siltuximab**

- FDA Approval: April 23, 2014
  - Treatment of patients with Multicentric Castleman’s Disease (MCD) who are HIV-negative and HHV-8-negative
  - Chimeric monoclonal antibody inhibitor of interleukin-6

**Siltuximab Mechanism and Dosing**

- Multicentric Castleman’s Disease
  - Dysregulated IL-6 production
  - Siltuximab
    - Binds with high affinity and specificity to IL-6 preventing interaction with IL-6 receptors
    - Does not bind to viral IL-6 produced by HHV-8
- Dosing
  - 11 mg/kg IV over 1 hour every 3 weeks
  - Continue until treatment failure

**Siltuximab Drug Interactions**

- CYP450 Substrates
  - Infection and inflammatory stimuli can downregulate CYP450 enzymes in the liver
  - IL-6 inhibition → restoration of CYP450 activity
  - Increased metabolism of CYP450 substrates

- Therapeutic drug monitoring
  - After initiation of siltuximab
  - After cessation of therapy

**Siltuximab for Multicentric Castleman’s Disease**

Efficacy and safety of siltuximab in patients with multicentric castleman’s disease.


- Design: Multicenter, randomized, double-blind, placebo-controlled phase 2 study
- Objective: To evaluate safety and efficacy of siltuximab in MCD
Siltuximab for Multicentric Castleman’s Disease

- **Randomization**: N = 53 Patients
- Siltuximab 11 mg/kg IV q3 wks + Best supportive care
- Durable tumor and symptomatic response

- **Randomization**: N = 26 Placebo + Best supportive care

79 Patients
- HIV- and HHV-8 negative MCD
- Symptomatic
- Newly diagnosed or pretreated

Siltuximab for MCD

**Endpoint**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Siltuximab + BSC (N = 53)</th>
<th>Placebo + BSC (N = 26)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable tumor and symptomatic response</td>
<td>34</td>
<td>0</td>
<td>0.0012</td>
</tr>
<tr>
<td>CR (%)</td>
<td>2</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>PR (%)</td>
<td>32</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Tumor response (%)</td>
<td>38</td>
<td>4</td>
<td>0.0022</td>
</tr>
<tr>
<td>Symptom response (%)</td>
<td>57</td>
<td>19</td>
<td>0.0087</td>
</tr>
<tr>
<td>Complete symptom resolution (%)</td>
<td>25</td>
<td>0</td>
<td>0.0037</td>
</tr>
<tr>
<td>Duration of durable tumor and symptomatic response (days)</td>
<td>383</td>
<td>--</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Siltuximab Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Siltuximab + BSC (n = 53)</th>
<th>Placebo + BSC (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>Grades 3-4 (%)</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>34</td>
<td>0</td>
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<tr>
<td>Grades 3-4 (%)</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Grades 3-4 (%)</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infections</td>
<td>36</td>
<td>2</td>
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<tr>
<td>Weight gain</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Grades 3-4 (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Grades 3-4 (%)</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Siltuximab Role in Therapy

<table>
<thead>
<tr>
<th>Pretreated</th>
<th>Treatment Naive</th>
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</thead>
<tbody>
<tr>
<td>Siltuximab</td>
<td>Placebo</td>
</tr>
<tr>
<td>(n = 29)</td>
<td>(n = 17)</td>
</tr>
<tr>
<td>Durable tumor and symptom response</td>
<td>34.5%</td>
</tr>
</tbody>
</table>

Prior Therapies
- Corticosteroids: 93.5%
- Cyclophosphamide: 50%
- Vincristine: 26.1%
- Rituximab: 17.4%

NEW DRUG UPDATE

Maurice D. Alexander, PharmD, BCOP, CPP
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University of North Carolina Medical Center/ North Carolina Cancer Hospital

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