Emerging Treatment Options for Relapsed/Refractory Hodgkin Lymphoma

Presented as a Live Webinar
Thursday, October 26, 2017
1:00 – 2:00 p.m. ET

On-demand Activity
Live webinar recorded and archived to be watched at your convenience
Available after November 29, 2017

www.ashpadvantage.com/go/hodgkinlymphoma

Provided by ASHP
Supported by an educational grant from Seattle Genetics, Inc.
Emerging Treatment Options for Relapsed/Refractory Hodgkin Lymphoma

Activity Overview

This educational activity will review the pathophysiology and etiology of classical Hodgkin lymphoma. Current and emerging treatments for newly diagnosed patients and for patients with relapsed or refractory disease will also be explained. The role of brentuximab vedotin in managing relapsed disease alone and in combination with other therapies will also be explained. In light of the potential for adverse effects and relapse, the activity will conclude with discussion of strategies for post-treatment monitoring.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Review the pathophysiology and etiology of classical Hodgkin lymphoma.
- Analyze the role of consolidation therapy with brentuximab vedotin following autologous stem cell transplant (SCT).
- Describe the role of PD-1 inhibitors in relapsed/refractory Hodgkin lymphoma.
- Review strategies for post-treatment monitoring for adverse events and relapse.

Continuing Education Accreditation

ASHP is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit.
Live activity ACPE activity #: 0204-0000-17-434-L01-P
On-demand activity #: 0204-0000-17-434-H01-P

Participants will process CPE credit online at http://elearning.ashp.org/my-activities. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of the live activity or completion of a home-study activity.

Webinar Information

Visit www.ashpadvantage.com/go/hodgkinlymphoma to find

- Webinar registration link
- Group viewing information and technical requirements
- CPE webinar processing information
Faculty

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Clinical Associate Professor
Assistant Director of Experimental Therapeutics
University of Florida College of Pharmacy
University of Florida Health Cancer Center
Gainesville, Florida

David L. DeRemer, Pharm.D., BCOP, FCCP, is Assistant Director of Therapeutics at the University of Florida Health Cancer Center (UFHCC) and practices in a Phase 1 research unit at the UFHCC in Gainesville, Florida. Dr. DeRemer received his Doctor of Pharmacy degree from the University of Kentucky in Lexington. He completed a pharmacy practice residency and hematology/oncology specialty residency at the University of Kentucky. He also completed an oncology/drug discovery fellowship at the University of Kentucky. Prior to this he was clinical associate professor and PGY-2 oncology residency program director at the University of Georgia College of Pharmacy in Augusta, Georgia. He is a board-certified oncology pharmacist with experience as both an inpatient and outpatient clinical specialist in bone marrow transplantation as well as leukemia/lymphoma clinics.

Dr. DeRemer has published extensively and presented nationally on oncology-related topics and topics related to treating patients with cancer.

Disclosures

In accordance with ACCME and ACPE Standards for Commercial Support, ASHP policy requires that all faculty, planners, reviewers, staff, and others in a position to control the content of this presentation disclose their relevant financial relationships.

- In this activity, no persons associated with this activity have disclosed any relevant financial relationships.
Emerging Treatment Options for Relapsed/Refractory Hodgkin Lymphoma

David L. DeRemer, Pharm.D., FCCP, BCOP
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Assistant Director of Experimental Therapeutics
University of Florida College of Pharmacy
University of Florida Health Cancer Center
Gainesville, Florida

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- Review strategies for post-treatment monitoring for adverse events and relapse.

Classical Hodgkin Lymphoma (cHL)

- Estimated 8260 new cases and 1070 deaths in 2017
- Bimodal distribution
  – Most cases 15-30 yo
  – ≥ 55 yo
- Highly curable >80%
- 20-30% of patients will relapse

**Pathology**

- cHL (95%)
  - Nodular sclerosis (75-80%)
  - Mixed cellularity
  - Lymphocyte depleted
  - Lymphocyte rich
- Nodular lymphocyte predominant (5%)


**Pathophysiology**

Frontline Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ABVD</th>
<th>Stanford V</th>
<th>BEACOPP (basic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug1</td>
<td>Doxorubicin 25 mg/m² IV days 1, 15</td>
<td>Doxorubicin 25 mg/m² IV days 1, 15</td>
<td>Bleomycin 10 units/m² IV day 8</td>
</tr>
<tr>
<td>Drug2</td>
<td>Bleomycin 10 units/m² IV days 1, 15</td>
<td>Vinblastine 6 mg/m² IV days 1, 15</td>
<td>Etoposide 100 mg/m² IV days 1-3</td>
</tr>
<tr>
<td>Drug3</td>
<td>Vinblastine 6 mg/m² IV days 1, 15</td>
<td>Mechlorethamine 6 mg/m² IV days 1</td>
<td>Doxorubicin 25 mg/m² IV day 1</td>
</tr>
<tr>
<td>Drug4</td>
<td>Dacarbazine 375 mg/m² IV days 1, 15</td>
<td>Vincristine 1.4 mg/m² IV days 1-3</td>
<td>Cyclophosphamide 650 mg/m² IV day 1</td>
</tr>
<tr>
<td>Repeat</td>
<td>Repeat every 28 days</td>
<td>Prednisone 40 mg PO QOD</td>
<td>Prednisone 100 mg/m² PO days 1-7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeat every 28 days</td>
<td>Prednisone 40 mg PO days 1-14</td>
</tr>
</tbody>
</table>


Unfavorable Risk Factors for Stage I-II

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>GHSG (German Hodgkin Study Group)</th>
<th>EORTC (European Organisation for Research and Treatment of Cancer)</th>
<th>NCCN (National Comprehensive Center Network)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 50 years</td>
<td>&gt;50 mm/hr if A</td>
<td>≥ 50 mm/hr or any B symptoms</td>
</tr>
<tr>
<td></td>
<td>&gt;50 mm/hr if A</td>
<td>&gt;50 mm/hr if A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50 mm/hr if B</td>
<td>&gt;30 mm/hr if B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;30 mm/hr if B</td>
<td></td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>MMR &gt; 0.33</td>
<td>MTR &gt; 0.35</td>
<td>MMR &gt; 0.33</td>
</tr>
<tr>
<td>Nodal sites</td>
<td>&gt;2</td>
<td>&gt;3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>E lesion</td>
<td>Any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulky</td>
<td></td>
<td></td>
<td>≥ 10 cm</td>
</tr>
</tbody>
</table>

MMR= Mediastinal mass ratio; MTR= Mediastinal thoracic ratio; ESR= Erythrocyte sedimentation rate

International Prognostic Score (IPS)  
Advanced Disease

- Albumin < 4g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Stage IV disease
- Age ≥ 45 years
- White blood count ≥ 15,000/mm³
- Lymphocyte count (<8% of WBC or <600/mm³)


The Renaissance of Hodgkin Lymphoma (HL)

**Historical**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is radiation therapy (RT) alone sufficient?</td>
<td>No, GHSG H7 (JCO 2007)</td>
</tr>
<tr>
<td>Is chemotherapy alone sufficient?</td>
<td>No, NCIC (NEJM 2012)</td>
</tr>
<tr>
<td>Since chemo + RT combination is needed...</td>
<td>30 years of studies</td>
</tr>
<tr>
<td>Which regimen?</td>
<td>ABVD vs. BEACOPP or Stanford V</td>
</tr>
<tr>
<td>How many cycles?</td>
<td></td>
</tr>
<tr>
<td>Dose and field of RT?</td>
<td></td>
</tr>
</tbody>
</table>

GHSG = German Hodgkin Study Group;  
NCIC = National Cancer Institute of Canada


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The Renaissance of Hodgkin Lymphoma (HL)

Contemporary
Could interim FDG-PET data minimize chemo cycles?
Yes, RAPID trial (NEJM 2015), EORTC 20051 (JCO 2014)

Could we use interim FDG-PET to adjust ABVD?
Yes, RATHL (NEJM 2016)

Does integration of novel agents in early stage unfavorable risk improve outcomes?
ECHELON -1 (ASH 2017)

Which agents to use to bridge to ASCT or treat refractory/relapsed disease?
The remainder of this talk.....

FDG-PET = fluorodeoxyglucose-positron emission tomography; EORTC= European Organisation for Research and Treatment of Cancer; ASH= American Society of Hematology; ASCT= autologous stem cell transplantation

Relapsed and Refractory HL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Agents</th>
<th>Reference</th>
</tr>
</thead>
</table>
Which of the following newly diagnosed patients has the best prognosis for cHL?

a. 18 yo male, Stage IA non bulky disease, ESR <30 mm/hr, one nodal mass 2 x 2 cm
b. 45 yo female, Stage IIB bulky disease, ESR 55, 3 nodal masses
c. 45 yo male, Stage IIIB, ESR 30, WBC 15K, albumin 3.9, smoking history – 30 pack years
d. 60 yo male, Stage IV disease, + B symptoms on diagnosis, mediastinal mass 6.5 x 6 cm

Brentuximab Vedotin

- Pharmacology
  - Anti-CD30 antibody conjugated with monomethyl auristatin E (MMAE)
  - Disruption of microtubule network
- Indications
  - Refractory cHL
    - Following failure of ASCT or at least 2 prior regimens
    - At high risk of relapse post-auto SCT consolidation
  - Refractory anaplastic large cell lymphoma
    - Failure of 1 prior multi-agent chemotherapy
- Contraindications
  - Concurrent bleomycin

Pivotal Phase II Trial


Phase II 5-year Follow-Up

Phase III - AETHERA

ELIGIBILITY
• Patients with cHL who achieved a CR, PR, or SD to salvage therapy prior to ASCT
  - Primary refractory (n=196, 60%)
  - Relapsed <12 months (n=107, 33%)
  - Extranodal disease prior to salvage chemo (n=107, 33%)

ENDPOINTS
• Primary: PFS
• Secondary: OS and safety

Brentuximab (BV) 1.8 mg/kg IV every 3 weeks (up to 16 cycles, 12 months) + Best supportive care (n=165)

Placebo (up to 16 cycles, 12 months) + Best supportive care (n=164)

Select Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BV (n=165)</th>
<th>Placebo (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of prior systemic salvage therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>57%</td>
<td>52%</td>
</tr>
<tr>
<td>&gt;2</td>
<td>43%</td>
<td>48%</td>
</tr>
<tr>
<td>Status after frontline therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory</td>
<td>60%</td>
<td>59%</td>
</tr>
<tr>
<td>Relapse &lt;12 months</td>
<td>32%</td>
<td>33%</td>
</tr>
<tr>
<td>Relapse &gt;12 months</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Best response to salvage post-ASCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>37%</td>
<td>38%</td>
</tr>
<tr>
<td>PR</td>
<td>35%</td>
<td>34%</td>
</tr>
<tr>
<td>SD</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>Pre-ASCT PET status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>39%</td>
<td>31%</td>
</tr>
<tr>
<td>Negative</td>
<td>34%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Efficacy Endpoints-AETHERA

**Subgroup Analysis**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>N</th>
<th>PFS (Independent Review)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>389</td>
<td>0.57 (0.40-0.81)</td>
<td>1.15 (0.67-1.97)</td>
</tr>
<tr>
<td>≥2</td>
<td>280</td>
<td>0.49 (0.34-0.71)</td>
<td>0.94 (0.53-1.67)</td>
</tr>
<tr>
<td>≥3</td>
<td>166</td>
<td>0.43 (0.27-0.68)</td>
<td>0.92 (0.45-1.88)</td>
</tr>
</tbody>
</table>


**Adverse Events**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>BV (n=167)</th>
<th>Placebo (n=160)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ Grade 3</td>
<td>≥ Grade 3</td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>56%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>10%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>0%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Peripheral motor neuropathy</td>
<td>6%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

Specific Findings

- **Peripheral neuropathy** – median onset 13.7 weeks (1-47.4); discontinuation 23%, dose modifications 31%
- **Neutropenia** – dose delays 22%
- **Severe infections** – 7% (BV)

Brentuximab Vedotin

• Demonstrated efficacy as salvage and consolidation therapy post-ASCT
• Emerging data as second-line agent
  – Phase II – 86% proceeded -> ASCT (65% mobilized with Cy+G-CSF)
• Favorable toxicity profile
• Combination trials
  – AVD + BV (1.2 mg/kg) -> Phase 3 ECHELON-1
    • FDA granted breakthrough therapy designation (10/2/17)
  – + Ibrutinib, + PD-1 inhibitor (nivolumab)

Cy+G-CSF = Cyclophosphamide + growth colony stimulating factor;
AVD +BV = doxorubicin, vinblastine, dacarbazine, brentuximab


Patient JC is a 49 yo female who was diagnosed with Stage III classical Hodgkin lymphoma 10 months ago. JC has completed ABVD x 6 cycles followed by IFRT as well as ICE (ifosfamide, carboplatin, etoposide) x 2 cycles. Post-treatment PET – Deauville score (4).
Which of the following treatments should be recommended?

a. Proceed to an allogenic stem cell transplant
b. Autologuous stem cell transplant followed by brentuximab 1.8 mg/kg IV Q21 days x 16 cycles
c. Maintenance brentuximab 1.8 mg/kg IV Q21 days until disease progression
d. Salvage bendamustine
PD-1 in Hodgkin Lymphoma

**Reed-Sternberg Cell**
- EBV infection
- 9p24.1 amplification
- JAK/STAT Activation
- PD-L1/2

**Macrophage**
- PD-L1

**T-cell**
- PD-1

**PD-1 Inhibitors**

- **Nivolumab**
  - Humanized IgG4 monoclonal antibody (MoAb) that binds to PD-1 blocking interaction with PD-L1 and PD-L2
  - FDA cHL indication
    - Relapsed or progressed after autologous HSCT (aHSCT) and BV or
    - 3 or more lines of therapy that includes auto HSCT
  - cHL dose – 3 mg/kg IV every 2 weeks

- **Pembrolizumab**
  - Humanized IgG4 MoAb that binds to PD-1 blocking interaction with PD-L1 and PD-L2
  - FDA cHL indication
    - tx of adult and pediatric patients who have relapsed after 3 or more lines of therapy
  - cHL dose – 200 mg IV every 3 weeks (adults); 2 mg/kg (up to 200 mg) IV every 3 weeks (pediatrics)

*HSCT=hematopoietic stem cell transplantation*
Phase I – CHECKMATE -039

**Design:** Dose escalation nivolumab (1-3 mg/kg) and expansion cohorts (3 mg/kg @ week 1, week 4, then Q2)

**1° objective - safety and toxicity**
**2° objective – efficacy and assessing PD-L1 ligand loci**

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>N=23 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>17%</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>70%</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>13%</td>
</tr>
<tr>
<td>Progression free survival (PFS) @24 weeks</td>
<td>86%</td>
</tr>
<tr>
<td>Overall survival (OS)</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR=Not reached

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**Phase II – CheckMate 205**

- **A** aHSCT failure and BV naïve (n=63)
- **B** aHSCT failure and post BV (n=80)
- **C** BV before & after aHSCT (n=100)
- **D** Newly diagnosed patients (+AVD) (n=50)

Nivolumab 3 mg/kg IV every 2 weeks (Cohorts A-C)
Nivolumab 240 mg IV every 2 weeks (Cohort D)

CheckMate 205 – Cohort B

<table>
<thead>
<tr>
<th>Specific baseline characteristics</th>
<th>n=80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>&gt;60 yo</td>
</tr>
<tr>
<td>Gender</td>
<td>M/F (64%/36%)</td>
</tr>
<tr>
<td>Disease stage at entry</td>
<td>III</td>
</tr>
<tr>
<td>IV</td>
<td>68%</td>
</tr>
<tr>
<td>B symptoms (present)</td>
<td>23%</td>
</tr>
<tr>
<td>Median previous lines of therapy</td>
<td>5 or more lines of therapy</td>
</tr>
<tr>
<td>Previous ASCT – one</td>
<td>93%</td>
</tr>
<tr>
<td>Previous ASCT - two</td>
<td>8%</td>
</tr>
<tr>
<td>Previous BV</td>
<td>After ASCT</td>
</tr>
<tr>
<td>No response to previous BV</td>
<td>54%</td>
</tr>
<tr>
<td>Time from completion to most recent NIVO tx</td>
<td>&lt;3 months</td>
</tr>
<tr>
<td>3-6 months</td>
<td>23%</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>23%</td>
</tr>
</tbody>
</table>


Cohort B Efficacy Endpoints

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>66% (54-76)</td>
<td>68% (56-78)</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>PR</td>
<td>58%</td>
<td>60%</td>
</tr>
<tr>
<td>SD</td>
<td>23%</td>
<td>NR</td>
</tr>
<tr>
<td>PD</td>
<td>8%</td>
<td>NR</td>
</tr>
<tr>
<td>Duration of response (months)</td>
<td>7.8 (6.6- NA)</td>
<td>13.1 (8.8-NA)</td>
</tr>
<tr>
<td>Duration of response (months)</td>
<td>4.6 (NA)</td>
<td>Not reached (4.6-NA)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>10 (8.4-NA)</td>
<td>14.8 (11.3 – NA)</td>
</tr>
</tbody>
</table>

CR= complete response; PR= partial response; SD= stable disease; PD= progressive disease; NA= not available; NR= not reported

9p24.1 Genetic Alterations


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**Phase II – KEYNOTE -087**

1. Post-ASCT and BV (n=69)

2. Post-salvage chemo and BV and ASCT ineligible (n=81)

3. Post-ASCT (n=60)

≥ 18 yo
Measurable dx (R/R HL)
ECOG 1 or 2
Adequate organ function

Endpoints
1° - ORR by BICR
2° - ORR by inv., PFS, duration of response, OS

Pembrolizumab 200 mg IV Q3 weeks for a maximum of 24 months

ORR=Overall response rates; BICR=Blinded independent central review; PFS=Progression free survival; OS=Overall survival

Duration of Response to Pembrolizumab


Overall Response to Pembrolizumab

<table>
<thead>
<tr>
<th>Response</th>
<th>Cohort 1 (n=69)</th>
<th>Cohort 2 (n=81)</th>
<th>Cohort 3 (n=60)</th>
<th>All Patients (n=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>73.9%</td>
<td>64.2%</td>
<td>70%</td>
<td>69% (62.3%-75.2%)</td>
</tr>
<tr>
<td>Complete remission</td>
<td>21.7%</td>
<td>24.7%</td>
<td>20%</td>
<td>22.4% (16.9%-28.6%)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>52.2%</td>
<td>39.5%</td>
<td>50%</td>
<td>46.7% (39.8%-53.7%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>16.9%</td>
<td>12.3%</td>
<td>16.7%</td>
<td>14.8% (10.3%-20.3%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7.2%</td>
<td>21%</td>
<td>13.3%</td>
<td>14.3% (9.9%-19.8%)</td>
</tr>
</tbody>
</table>

## PD-1 Inhibitor Toxicity

<table>
<thead>
<tr>
<th>Checkmate (G3/4 (%))</th>
<th>Keynote</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRAE (G3/4) (%)</strong></td>
<td><strong>-039 (n=23)</strong></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0 1 0 0.5</td>
</tr>
<tr>
<td>Cough</td>
<td>0 NR NR 0.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 0 0 0.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 0 0 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>NR NR NR 0.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>NR 5 5 2.4</td>
</tr>
<tr>
<td>Rash</td>
<td>0 3 1 0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 0 0 0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>NR 3 1 1</td>
</tr>
</tbody>
</table>

**Note:**
- **TRAE=** Treatment related adverse event; CB= Cohort B; NR= Not reported.

**References:**

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## PD-1 Inhibitors Post-Transplant

- **Autologous**
  - Provide ORR in R/R cHL post-ASCT
  - Therapeutic value as a post-auto consolidation option?

- **Allogeneic**
  - ↑T-cell activation -> worsening GVHD, other immune complications?
  - FDA “Warning and Precaution” on 5/7/2016
  - Nivolumab
    - N=17 (15 RIC, 2 myeloablative)
    - 35% died from complications of allo SCT (5 deaths in severe GVHD setting)
    - Steroid requiring febrile syndrome in 6 patients
    - VOD occurred in 1/17

**Notes:**
- RIC= reduced intensity conditioning;
- VOD= veno occlusive disease

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PD- 1 Inhibitors

- Excitement and further questions.....
- Identification of novel biomarker?
- Favorable toxicity profile
- Infinite number of promising combination trials ongoing
  - Frontline – N+AVD, N+BV
  - R/R – BV, ibrutinib, lenalidomide, IFRT

Post-Treatment Monitoring
**Monitoring Post-Treatment Completion**

- **Physical exam**  
  - Every 3-6 months for 1-2 years then every 6-12 months
- **Lab evaluation**  
  - CBC, platelets, ESR, TSH (at least annual if RT)
- **Imaging**  
  - CT with contrast – neck/chest/abdomen/pelvis @ 6, 12, and 24 months  
  - PET/CT only if last PET + (Deauville 4-5)
- **Counseling**  
  - Reproduction, cardiovascular, cancer screening recommendations

CBC=complete blood count; ESR=erythrocyte sedimentation rate; TSH=thyroid-stimulating hormone; CT=computed tomography


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**Immune Mediated Toxicities**

- **Dermatologic**
- **Gastrointestinal**
- **Endocrine**  
  - Hypophysitis, adrenal, thyroid
- **Hepatic**
- **Pulmonary**
- **Renal**
- **Pancreatic**
- **Neurologic**
Monitoring and Evaluations

- Patient education
  - Information sources – pamphlets, guides
- Baseline and ongoing assessments
  - Organ specific toxicity
- Documentation
  - NCI Common Toxicity Criteria (NCI-CTCAE v4.0)

Management Strategies for Toxicity

Grade 1
- Continue immunotherapy
- Treatment of symptoms

Grade 2
- Delay therapy and restart when symptoms improve
- Consider glucocorticosteroids 0.5-1 mg/kg/day

Grade 3/4
- Discontinue immunotherapy (except in patient with skin or endocrine toxicities)
- Give glucocorticosteroids 1-2 mg/kg/day
- Consider hospitalization


Patient AB was diagnosed with Stage IIIB cHL and subsequently received (ABVD x 6, ICE x 2) followed by ASCT + brentuximab x 7 cycles. Repeat FDG-PET demonstrated progressive disease and nivolumab was initiated for 4 cycles. Patient has complained of worsening cough and ground glass opacities were noted on imaging. Grade 2 immune related pneumonitis is diagnosed. What is your recommendation?

a. Monitor and document current patient disposition
b. Initiate corticosteroids at 1-2 mg/kg/day followed by taper
c. Permanently discontinue nivolumab
d. Switch patient to pembrolizumab

Vaccinations

- Annual influenza vaccination
- Concurrent anti-PD-1 therapy
  - Laubil HP et al. (J Clin Oncol 35, 2017, abs #14523)
    - Median time between PD-1 initiation and vaccination 74 days (44-57)
    - 12 patients (52%) experienced immune related AE (irAE)
    - Colitis (n=2), encephalitis (n=1), vasculitis (n=1), pneumonitis (n=1)
  - Kanaloupitis DM et al. (J Clin Oncol 35, 1017, abs #14607)
    - No grade 3/4 imAEs were noted
Conclusions

• Treatment options for R/R cHL has evolved significantly
• Therapies in refractory -> frontline?
• Emergence of biomarker to predict responders?
• Novel agents in the setting of transplant

Which of these practice changes will you consider making?

• Discuss with colleagues the pathophysiology and etiology of classical Hodgkin lymphoma.
• Educate staff on the role of consolidation therapy following autologous stem cell transplant (SCT).
• Discuss with colleagues strategies for post-treatment monitoring for adverse events and relapse in patients with Hodgkin lymphoma.
• Incorporate the most current evidence-based guidelines into practice when treating patients with Hodgkin lymphoma.
• Educate staff on the different classes of drugs used to treat Hodgkin lymphoma, and the pharmacokinetics, pharmacodynamics, adverse effects, precautions, warnings, and contraindications of each.
• Discuss with colleagues the risk factors associated with relapsed/refractory Hodgkin lymphoma.