Bleomycin versus Brentuximab in Hodgkin Lymphoma: Don’t Hold Your Breath

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January 8th, 2019
Objectives

1. Explain the current standard of care for classical Hodgkin Lymphoma

2. Describe brentuximab vedotin’s place in therapy for Hodgkin Lymphoma

3. Identify strategies used to minimize long term effects of therapy for Hodgkin Lymphoma
Background - Lymphoma

Lymphoma

Non-Hodgkin Lymphoma
- 4.3% of all new cancers
- 74,680 new cases
- >60 different types
- Majority have B-cell involvement

Hodgkin Lymphoma
- 0.5% of all new cancers
- 8,500 new cases
- Classical (95%) and nodular lymphocyte predominant (5%)
  - 4 subtypes of Classic Hodgkin Lymphoma (cHL)
  - Reed-Sternberg cells

Both are cancers of the cells in the lymphatic system generally manifesting in the lymph nodes

Cancer Stat Facts: Hodgkin Lymphoma. NIH National Cancer Institute 2018
Cancer Stat Facts: Non-Hodgkin Lymphoma. NIH National Cancer Institute 2018
Hodgkin Lymphoma Epidemiology

- Bimodal disease onset
  - 15 – 30 years old and >55 years old
- Males > females
- 8,500 new cases and 1,050 deaths annually
- 86.6% 5 year overall survival rate
  - One of the most curable types of cancer
  - Long-term adverse events from therapy are becoming a problem due to extended survival of cHL patients
Hodgkin Lymphoma History

• First described by Sir Thomas Hodgkin in 1832
  • Enlarged lymph nodes and spleen, contiguous spread

• Around 1900, Carl Sternberg and Dorothy Reed described the “diagnostic” cells of Hodgkin’s
  • Presence of Reed-Sternberg cells are used to diagnose Hodgkin’s in combination with the immunophenotype (cell markers) displayed by the cell
Pathology

• Reed-Sternberg Cells
  • Clonally derived from B-cells but typical B-cell markers are generally absent
  • Express CD30 – usually limited to a minority of activated B cell, T cells, and eosinophils
  • Only make up 1-2% of the tumor mass

• Remaining tumor environment
  • Composed of inflammatory cells: T cells, histiocytes, neutrophils, eosinophils, plasma cells, fibroblasts
### Presentation and Symptoms

<table>
<thead>
<tr>
<th>“B-Symptoms”</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Unexplained fevers &gt; 38°C</td>
</tr>
<tr>
<td>• Drenching night sweats</td>
</tr>
<tr>
<td>• Weight loss &gt; 10% body weight within 6 months of diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pruritus</td>
</tr>
<tr>
<td>• Fatigue</td>
</tr>
<tr>
<td>• Cough</td>
</tr>
<tr>
<td>• Chest pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lymph node enlargement</td>
</tr>
<tr>
<td>• May or may not be painful</td>
</tr>
</tbody>
</table>

PET = positron emission tomography

©2017 MFMER | slide-7
Diagnosis

• Excisional lymph node biopsy preferred
  • Avoid fine needle biopsy

• Immunohistochemistry
  • Expression of CD15 and CD30 on Reed-Sternberg cells
  • Also CD3, CD45, CD79a, PAX5
  • <40% will be CD20 positive in cHL

• PET scan
  • Performed for sizing, location, and staging
  • Sometimes done with CT scan

PET = positron emission tomography
CT = computed tomography
Staging – Ann Arbor Staging System

Any involvement in the liver, bone marrow, or CSF is automatically stage IV.

Further broken down into “A” meaning no B symptoms, and “B” meaning presence of B symptoms.
Staging and Re-Staging– Deauville Criteria

• PET scan performed at baseline, interim during treatment, and at end of treatment

• Disease response based on assessment of fluorodeoxyglucose (FDG) uptake in the involved sites

<table>
<thead>
<tr>
<th>Deauville Score</th>
<th>Definition</th>
<th>Interpretation (Interim Scan)</th>
<th>Interpretation (Final Scan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>No or decreased uptake</td>
<td>Complete metabolic response (CMR)</td>
<td>CMR</td>
</tr>
<tr>
<td>3</td>
<td>Less than surrounding tissues</td>
<td>Stable vs. responding</td>
<td>Likely CMR</td>
</tr>
<tr>
<td>4-5</td>
<td>Increased or new uptake</td>
<td>Partial metabolic response (PMR)</td>
<td>No response or progression</td>
</tr>
</tbody>
</table>
International Prognostic Score (IPS)

- Used for prognosis prediction and treatment guidance for stage III-IV disease
- Defined by risk factors present at diagnosis
  - ≥45 years old
  - Male
  - Stage IV disease
  - Albumin <4 g/dL
  - Hgb < 10.5 g/dL
  - WBC >15,000/mm³
  - Lymphocyte count <8% of the WBC count (or ALC<600)

Score 0-2: 86% 5-year OS
Score >2: 70% 5-year OS


Hgb = hemoglobin
WBC = white blood cell
OS = overall survival
Overall treatment course – Advanced cHL

Initial Treatment

Chemotherapy for ~2 cycles
PET scan restaging
Response Chemo x 4 cycles
PET
Observe +/- ISRT

Relapsed/Refractory Disease

Different chemotherapy
PET scan
Conditioning therapy and SCT +/- ISRT
Observe vs. therapy

cHL = Classic Hodgkin Lymphoma
PET = positron emission tomography
ISRT = involved site radiation therapy
SCT = stem cell transplant
Common Initial Treatment Regimens (cHL)

**ABVD**
- Doxorubicin (Adriamycin®)
- Bleomycin
- Vinblastine
- Dacarbazine

**Stanford V**
- Doxorubicin
- Bleomycin
- Vinblastine
- Mechlorethamine
- Vincristine

**BEACOPP**
- Doxorubicin
- Bleomycin
- Vincristine
- Procarbazine
- Cyclophosphamide
- Etoposide
- Prednisone

*Better PFS only (no OS benefit)*
*Increased toxicities*
**ABVD Regimen**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Doxorubicin</td>
<td>25 mg/m² IV Day 1, 15</td>
</tr>
<tr>
<td>B</td>
<td>Bleomycin</td>
<td>10 units/m² IV Day 1, 15</td>
</tr>
<tr>
<td>V</td>
<td>Vinblastine</td>
<td>6 mg/m² IV Day 1, 15</td>
</tr>
<tr>
<td>D</td>
<td>Dacarbazine</td>
<td>375 mg/m² IV Day 1, 15</td>
</tr>
</tbody>
</table>

- Regimen developed in 1975 and has been the standard of care
- Important to maintain dose intensity for best response despite neutropenia that occurs

**Cycle duration:** 28 days

**2-6 cycles depending on stage**
### Bleomycin – Pulmonary Toxicity

**Mechanism**
- Bleomycin forms a complex with iron which causes free radical production in the presence of oxygen in the lungs leading to DNA strand breaks and cell death.

**Onset**
- Injury happens gradually after bleomycin administration and may present up to several months later.
- Overall 10-25% will develop pulmonary toxicity.

**Presentation**
- Fever, dyspnea, cyanosis, pleuritic pain, rales.
- Interstitial pneumonitis → pulmonary fibrosis.
- 1-3% mortality rate.

**Risk Factors**
- Age>40, mediastinal radiation, cumulative dose (>300 units), renal insufficiency, underlying lung disease, tobacco history, concomitant G-CSF use (controversial).

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Sleiffer S. *CHEST* 2001;120:617-624
Question 1

Which drugs compose the backbone of ABVD?

A. Adriamycin, Cyclophosphamide, vincristine, Dexamethasone

B. Azacitadine, Busulfan, Velcade, Daunorubicin

C. Abraxane, Bleomycin, Vinorelbine, Dexamethasone

D. Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
Brentuximab
Brentuximab Vedotin Mechanism of Action

Antibody drug conjugate

Monomethyl Auristatin E (MMAE)

Protease-cleavable linker

Anti-CD30 monoclonal antibody

Cytoxic!

Mitotic Spindle

Lysosome

CD30
Brentuximab FDA Approval Timeline for cHL

- **08/19/2011**: Relapsed/refractory (2 treatment failures or SCT failure)
- **08/18/2015**: Post-SCT consolidation
- **03/20/2018**: Previously untreated advanced cHL

**Single-Agent Dosing:**
1.8 mg/kg IV every 3 weeks (180 mg max)

**Combination Dosing:**
1.2 mg/kg IV every 2 weeks (120 mg max) in combination with AVD

SCT = stem cell transplant
AVD = doxorubicin, vinblastine, dacarbazine
Brentuximab in Relapsed/Refractory cHL

**Initial Treatment**

Chemotherapy for ~2 cycles → PET scan restaging → Response Chemo x 4 cycles → PET Observe +/- ISRT

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**Relapsed/Refractory Disease**

Different chemotherapy → PET scan → Conditioning therapy and SCT +/- ISRT → Observe vs. therapy

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*cHL = Classical Hodgkin Lymphoma
PET = positron emission tomography
ISRT = involved site radiation therapy
SCT = stem cell transplant*
Phase I Trial – Relapsed/Refractory

Brentuximab vedotin for relapsed CD30-positive lymphomas (Younes, et al. NEJM 2010)

| Design | Open-label, phase 1, dose-escalation study |

**Design**
Open-label, phase 1, dose-escalation study

**Patients**
- 45 patients, relapsed/refractory, CD30+ hematologic cancers
- Median 3 previous therapies, 73% prior auto-SCT

**Intervention**
Brentuximab monotherapy: 0.1-3.6 mg/kg every 3 weeks

**Maximum Tolerated Dose (MTD)**
- MTD = 1.8 mg/kg every 3 weeks

**Results**
- Primary endpoint = objective response (CR + PR)
- 17/45 had an objective response (6/12 of 1.8 mg/kg patients)
- 86% regression of tumor, duration of response = 9.7 months

**Safety**
- Fatigue, diarrhea, nausea, neutropenia, peripheral neuropathy (36%)

**Conclusion**
Brentuximab use resulted in durable, objective responses or tumor regression in most relapsed/refractory patients

Auto-SCT = autologous stem cell transplant
MTD = Maximum tolerated dose
CR = complete remission, PR = partial remission

Phase II Trial – Relapsed/Refractory

- Multinational, open-label, phase II study

Relapsed or refractory Hodgkin’s lymphoma after auto-SCT

≥12 years old, ECOG 0-1
71% relapsed within one year of SCT

Brentuximab 1.8 mg/kg
IV every 3 weeks
Max: 16 cycles

N=102

Auto-SCT = autologous stem cell transplant
ECOG = Eastern Cooperative Oncology Group

### Phase II Trial – Endpoints

#### Primary Endpoint

| Objective response rate (ORR) | 75% (median time 5.7 weeks) |

#### Secondary Endpoints

<table>
<thead>
<tr>
<th>Complete response (CR)</th>
<th>34% (median time 12 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression free survival (PFS)</td>
<td>5.6 months (objective response), 21.7 months (CR)</td>
</tr>
</tbody>
</table>

#### 3 and 5 Year Follow-up Data

<table>
<thead>
<tr>
<th>Overall survival (OS)</th>
<th>3 years: 73% (median 40.5 months)</th>
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<tbody>
<tr>
<td></td>
<td>5 years: 41%</td>
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</table>
## Phase II Trial – Safety

### Safety

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Peripheral Neuropathy</td>
<td>42% (≥ grade 3 = 8%), median onset 12.4 weeks 9/20 discontinuations due to neuropathy 50% had complete resolution</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>≥ grade 3 = 20%, none febrile 16% of dose delays due to neutropenia</td>
</tr>
</tbody>
</table>

### 3-year Follow-up Data – Significant favorable prognostic factors

| Univariate Analysis | Younger, good performance status, lower disease burden                     |

**Conclusion**: Prolonged PFS was seen in patients that achieved a CR with brentuximab in the relapsed/refractory setting. Significant peripheral neuropathy may guide the duration of treatment with more fit patients doing better overall.
Brentuximab for Initial Therapy in cHL

Initial Treatment

Chemotherapy for ~2 cycles
PET scan restaging
Response Chemo x 4 cycles
PET
Observe +/- ISRT

Relapsed/Refractory Disease

Different chemotherapy
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## Phase I Trial – Newly Diagnosed Combination Study

Brentuximab combined with ABVD or AVD for patients with newly diagnosed Hodgkin’s Lymphoma (Younes, et al. Lancet Oncol 2013)

| Design | Open-label, phase 1, dose-escalation study |

**BV** = Brentuximab  
**MTD** = Maximum tolerated dose  
**ILD** = interstitial lung disease  
**ABVD** = doxorubicin, bleomycin, vinblastine, dacarbazine  
**AVD** = doxorubicin, vinblastine, dacarbazine
Phase III Trial - ECHELON-1 Trial

- International, open-label, randomized, multicenter, phase 3 trial

Randomize

Adult patients with advanced Classic Hodgkin Lymphoma (Ann Arbor stage III or IV)

No previous treatments

N=664

AVD + BV
(1.2 mg/kg IV Q2 weeks)

N=670

ABVD

Treated for up to 6 cycles

At cycle 2 day 28, a PET scan was done to determine continuation vs. switching regimens based on Deauville score

Stratified according to IPS risk group

BV = Brentuximab
ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine

Inclusion/Exclusion and Dose Adjustments

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>• ECOG 0-2</td>
<td>• Nodular lymphocyte predominant HL</td>
</tr>
<tr>
<td>• ANC&gt;1500/mm³, platelets &gt;75,000/mm³, Hgb&gt;8 g/dL</td>
<td>• Peripheral sensory or motor neuropathy</td>
</tr>
<tr>
<td>• Tbili&lt;1.5xULN, AST/ALT&lt;3xULN</td>
<td>• Known cerebral or meningeal disease</td>
</tr>
<tr>
<td>• SCr&lt;2, CrCl&gt; 40mL/min</td>
<td>• Clinically relevant cardiovascular conditions</td>
</tr>
</tbody>
</table>

Dose Adjustments

• Peripheral neuropathy
  • Allowed decrease to 0.9 mg/kg, ≥ grade 3 consider holding

• Neutropenia
  • ≥ Grade 3 managed with growth factors per institutional policy
ECHELON-1 Trial Endpoints

Primary Endpoint
- Modified progression free survival (m-PFS) = time without disease progression, death, or modified progression (subsequent therapy)
- Failure to obtain a “good enough” response after primary therapy

Secondary Endpoint
- Overall survival = time from randomization to death from any cause
- Overall response rate, rate of CR
- Adverse events

Patients
- 58% men, median age 36
- 64% stage IV disease, mostly ECOG score 0-1
- Mean duration 5.6 cycles, median follow-up 24.6 months

ECHELON-1 Trial Results

• Intention-to-treat population, a priori alpha set at 0.025

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>82.1% (BV group) vs. 77.2% (HR 0.77, p = 0.04)</th>
</tr>
</thead>
<tbody>
<tr>
<td>m-PFS (at 2 years)</td>
<td>Absolute risk reduction = 4.9%</td>
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</table>

<table>
<thead>
<tr>
<th>Secondary Endpoints</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (at 2 years)</td>
<td>96.6% vs. 94.2% (HR 0.73, p = 0.20)</td>
</tr>
<tr>
<td></td>
<td><em>Waiting for updated results</em></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>37% (BV group) vs. 28% (ABVD)</td>
</tr>
<tr>
<td>Death</td>
<td><strong>ABVD</strong>: 39 deaths, 13 during treatment (<strong>11 due to pulmonary toxicity</strong>)</td>
</tr>
<tr>
<td></td>
<td><strong>BV</strong>: 28 deaths, 9 during treatment (<strong>7 neutropenia, 2 MI</strong>)</td>
</tr>
</tbody>
</table>
## ECHELON-1 Safety and Conclusions

### Safety (no p-values reported) – BV + AVD vs. ABVD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
</table>
| Neutropenia                            | • Grade ≥3: 70% vs. 50% (21% vs 8% febrile)  
• More common in >60 years old, earlier cycles  
• Led to use of G-CSF ppx for last 25% of patients enrolled in BV arm which lowered FN rate to 11% |
| Peripheral Neuropathy                  | • All: 67% vs. 43%  
• Grade ≥3: 11% vs. 2%  
• 10% vs. 4% discontinuation rate  
• 43% resolved upon discontinuation |
| Pulmonary toxicity                     | 2% vs. 7%                                                                                                                                 |

- No significant difference in m-PFS when brentuximab replaces bleomycin
- Increased rates of hospitalization, febrile neutropenia, and neuropathy but less pulmonary toxicity
- Overall survival data pending \(\rightarrow\) may guide place in therapy
- Major limitation: PET-directed therapy was not incorporated
Cost-Effectiveness Analysis of Brentuximab

• Used data from ECHELON-1 trial to create a Markov decision-analytic model to assess the benefit of brentuximab compared to standard therapy

• Payer perspective → drug acquisition costs based on Medicare/Medicaid average sales prices

• **QALY** = Quality-Adjusted Life-Years
  • Outcomes assessed based on enhanced survival and enhanced quality of life
    • 1 = perfect year of health, 0 = death
    • Mobility, self-care, usual activities, pain, anxiety/depression
Definitions

- **CER** = Cost-effectiveness Ratio
  - Cost of an intervention per year of quality life gained – allows for comparison
  - Ex: $20,000 annual cost, provides 4 QALY’s = CER of $20,000 / 4 = $5,000 per QALY

- **ICER** = Incremental Cost-effectiveness Ratio
  - Difference between two “CER” values = additional cost to gain one more QALY year with one intervention
  - Cost of “gained effectiveness”

- Common ICER threshold for drugs in economic studies is $100,000 to $150,000 dollars per QALY
  - Societal “willingness to pay” = 1-3 times GDP per capita
## Results

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Lifetime Health Care Cost</th>
<th>Incremental Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD</td>
<td>$184,291</td>
<td>$176,846</td>
</tr>
<tr>
<td>AVD + BV</td>
<td>$361,137</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>QALY (Effectiveness)</th>
<th>Incremental QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD</td>
<td>19.30</td>
<td>0.56</td>
</tr>
<tr>
<td>AVD + BV</td>
<td>19.86</td>
<td></td>
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\[
ICER = \frac{176,846}{0.56} = 317,254
\]

To meet the ICER of $100,000 to $150,000, would need to decrease the acquisition cost by 73% and 56% respectively.
Brentuximab in Stem Cell Transplant for cHL

**Initial Treatment**

1. Chemotherapy for ~2 cycles
2. PET scan restaging
3. Response Chemo x 4 cycles
4. PET Observe +/- ISRT

**Relapsed/Refractory Disease**

1. Different chemotherapy
2. PET scan
3. Conditioning therapy and SCT +/- ISRT
4. Observe vs. therapy

**Acronyms**
- cHL = Classical Hodgkin Lymphoma
- PET = positron emission tomography
- ISRT = involved site radiation therapy
- SCT = stem cell transplant
AETHERA trial – Study Design

- Phase 3, randomized, double-blind, placebo-controlled

Adult patients with relapsed or primary refractory HL post auto-SCT

No prior brentuximab and considered “high risk”

N=165

Brentuximab 1.8 mg/kg IV Q3 weeks x16 cycles

N=164

Placebo

Risk Factors: primary refractory, relapse < 12 months, extranodal involvement, two or more previous salvage therapies, no CR to most recent therapy

Stratified by:
- Response after salvage chemo (CR vs PR vs stable)
- Primary refractory versus relapse <12 or >12 months after therapy

AETHERA trial - Results

<table>
<thead>
<tr>
<th>Five-Year Updated PFS</th>
<th>Brentuximab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression Free Survival (PFS) (Investigator reviewed)</td>
<td>Not reached</td>
<td>15.8 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59% vs 41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 0.521</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Endpoints</th>
<th>Brentuximab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (OS)</td>
<td>(interim analysis) HR 1.15, p = 0.62</td>
<td><em>85% of placebo patients later got brentuximab off-study</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Sensory Neuropathy</td>
<td>Grade ≥3: 10% vs 1%</td>
<td>23% discontinuation, 31% dose modification</td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade ≥3: 29% vs 10%</td>
<td>25% vs. 11% received growth factor support</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7% vs. 6% grade 3 infections</td>
</tr>
<tr>
<td>Pulmonary effects</td>
<td>5% vs. 3%, 2 related deaths in brentuximab group</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion and Questions Remaining

- **Conclusion**: Brentuximab consolidation after auto-SCT significantly improved PFS for high-risk HL patients

- Overall survival benefit?
  - Too early to tell, high-amount of cross-over in study

- Quality of life impact?
  - One study showed peripheral neuropathy did not significantly impact quality of life in this setting

- If brentuximab is used prior to auto-SCT, can it still be used post-transplant with similar results?
  - Study with 21 HL patients showed objective response rate of 60% (30% CR), higher rate of peripheral neuropathy due to cumulative exposure

Auto-SCT = autologous stem cell transplant
HL = Hodgkin Lymphoma

Question 2

Based on the data we have discussed, which patient below would be most appropriate to incorporate brentuximab as part of their therapy?

A. 27 year old female with relapsed stage IV disease who complains of peripheral neuropathy from previous therapy

B. 25 year old male with stage III newly diagnosed disease with a history of severe asthma

C. 61 year old female diagnosed with stage I Hodgkin Lymphoma with no other comorbidities

D. 31 year old male receiving an auto-stem cell transplant who had five years without relapse of his disease
Brentuximab place in therapy?

- Front-line therapy
  - Higher risk patients (Stage III-IV disease, extranodal involvement, poor prognosis)
  - Strong desire to avoid even the potential for pulmonary toxicity
  - Drug cost is carefully considered

- Relapsed/refractory
  - Reasonable in this setting

- Stem cell transplant
  - Patients at a high risk of relapse (primary refractory, relapsed in less than 12 months, extranodal involvement pre-transplant)
Strategies to Avoid Toxicity
PET-directed therapy in cHL

- Is there a time when you can safely remove Bleomycin from ABVD without losing efficacy?

Chemotherapy for ~2 cycles → PET scan re-staging → Response Chemo x 4 cycles → PET → Observe +/- ISRT

cHL = Classical Hodgkin Lymphoma
PET = positron emission tomography
ISRT = involved site radiation therapy
PET-Directed Therapy – RATHL study

• Prospective, randomized, non-inferiority trial

Adult patients with advanced HL stage IIA to IV.
All received 2 cycles of ABVD.

Interim PET-CT

N=937

Negative Score:
1 (no uptake)
2 (slight uptake)
3 (equal or slightly above)

Randomize

N=470
ABVD x 4 more cycles

N=465
AVD (no bleomycin) x 4 cycles

N=182

Positive Score:
4 (moderately higher)
5 (markedly higher)

Intensified therapy
(BEACOPP)

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine
AVD = doxorubicin, vinblastine, dacarbazine
RATHL Study Results and Conclusion

### Primary Endpoint

<table>
<thead>
<tr>
<th>Progression free survival at 3 years (PFS)</th>
<th>ABVD</th>
<th>AVD</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>85.7%</td>
<td>84.4%</td>
</tr>
<tr>
<td></td>
<td>HR 1.13 (95% CI 0.81 – 1.57), p=0.48</td>
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<tr>
<td></td>
<td>Difference = 1.6% (CI -3.2 to 5.3)</td>
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</tbody>
</table>

**Upper boundary >5% cut-off** (calculated with higher anticipated survival)

### Secondary Endpoints

<table>
<thead>
<tr>
<th>3 Year Overall survival</th>
<th>ABVD</th>
<th>AVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>97.2%</td>
<td>97.6%</td>
<td></td>
</tr>
</tbody>
</table>

| Any pulmonary event     | 15 (3%) | 3 (1%) |

**Conclusion:** Removing bleomycin after two cycles with negative PET-CT had minimal risk of treatment failure, no survival difference, and reduced toxicity

Impact of PET-Directed Therapy

• Strategy has been incorporated into “Ask Mayo Expert” online and is an approach frequently used by providers at Mayo

• Must acknowledge the subjective nature of reading these PET-CT’s and the lack of overall survival data at this time

• Provides a strategy to potentially reduce the unfortunate long-term pulmonary toxicity associated with ABVD

Question 3

Which strategy or strategies below minimize adverse effects of Hodgkin Lymphoma therapy?

A. Using PET-directed therapy to eliminate bleomycin after cycle 2
B. Use of brentuximab to avoid bleomycin pulmonary toxicity
C. Decreasing treatment doses to minimize neutropenia when a patient is neutropenic with a previous cycle
D. A and B
E. A and C
Summary

• Standard of care for Hodgkin Lymphoma in most patients is still ABVD

• Some patients may benefit from brentuximab as part of their regimen but the benefits and costs must be weighed with each patient
  • Brentuximab has several FDA-indications – consider the data before adding to therapy

• The development of PET-directed therapy has changed the way ABVD is used in practice and has the potential to greatly impact quality of life
Questions & Discussion
Supplemental Slides
# ABVD Toxicities

<table>
<thead>
<tr>
<th>Medication</th>
<th>Toxicities</th>
</tr>
</thead>
</table>
| **Adriamycin** (Doxorubicin)| - Acute and delayed cardiotoxicity  
                              - Hematologic toxicities, secondary malignancies  
                              - Discoloration of bodily secretions |
| **Bleomycin**               | - Pulmonary toxicity  
                              - Vascular toxicities (CVA, MI, HUS)  
                              - Dermatologic reactions |
| **Vinblastine**             | - Peripheral Neuropathy  
                              - Vascular toxicities (CVA, MI)  
                              - Cytopenias |
| **Dacarbazine**             | - Nausea/vomiting  
                              - Alopecia  
                              - Myelosuppression |
Brentuximab

Hodgkin Lymphoma Indications
- Relapsed/refractory (2 treatment failures or SCT failure)
- Consolidation therapy post-stem cell transplant
- Previously untreated Hodgkin Lymphoma

Dose
- Single agent: 1.8 mg/kg IV every 3 weeks (max 180 mg)
- Combination: 1.2 mg/kg IV every 2 weeks (max 120 mg)
- Avoid use in CrCl<30 mL/min and Child-Pugh class B or C

Adverse Effects
- Peripheral neuropathy (dose reduction, sometimes permanent)
- Prolonged neutropenia (>1 week), infection
- Contraindicated to use with bleomycin due to pulmonary toxicity

SCT = stem cell transplant

## Cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>AWP x 70 kg patient (BSA 1.85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>$127 (per 30 units) x 10 units/m² = $127 x 6 cycles = $762</td>
</tr>
<tr>
<td>Brentuximab</td>
<td>$8,850 (per 50mg) x 1.2 mg/kg = $17,700 x 6 cycles = $100,000</td>
</tr>
<tr>
<td>Costs</td>
<td>Baseline (US$)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Brentuximab vedotin (per 50-mg vial)</td>
<td>6,970</td>
</tr>
<tr>
<td>AVD per dose</td>
<td>3,822</td>
</tr>
<tr>
<td>ABVD per dose</td>
<td>3,896</td>
</tr>
<tr>
<td>Filgrastim (300 µg, 5 doses)</td>
<td>1,073</td>
</tr>
<tr>
<td>Pegylated filgrastim (per dose)</td>
<td>4,321</td>
</tr>
<tr>
<td>Consolidative radiation</td>
<td>19,886</td>
</tr>
<tr>
<td>Salvage chemotherapy</td>
<td>45,987</td>
</tr>
<tr>
<td>ASCT</td>
<td>130,698</td>
</tr>
<tr>
<td>Allo-SCT</td>
<td>258,985</td>
</tr>
<tr>
<td>Nivolumab (per 100-mg vial)</td>
<td>2,680</td>
</tr>
<tr>
<td>Lymphoma-related end-of-life care</td>
<td>54,561</td>
</tr>
<tr>
<td>Nonlymphoma end-of-life care</td>
<td>43,578</td>
</tr>
<tr>
<td>Routine clinic visit</td>
<td>119</td>
</tr>
<tr>
<td>Intravenous chemotherapy administration, up to 1 hour</td>
<td>145</td>
</tr>
</tbody>
</table>
Before

PET

CT

PET/CT