Hodgkin Lymphoma
Management Updates 2017

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I receive grant/research support from Seattle Genetics and Millennium. I am also a consultant for Seattle Genetics, Genentech and Merck. I am on the Speaker’s Bureau for Seattle Genetics, Genentech and Millennium.
Overview

- Case presentation
- Background
- Prognostic factors
- Upfront treatment
- Relapsed/refractory
- Auto-HCT/Allo-HCT
- Novel therapies clinical trials
Case presentation

- A 25 year old female right cervical LAD
- No fever, chills, night sweats
- Cough, and SOB with exertion/cough
- PE: right cervical
- LAB: elevated ESR
- FDG-PET scan. The scan shows increased SUV uptake and discrete masses in the right cervical, right supraclavicular, mediastinal (nonbulky), and pretracheal LAD.
- Pathology: classical HL, nodular sclerosing type, CD30 +
- This patient was diagnosed with stage IIA Hodgkin lymphoma.
Background

- ~9000 new cases in the US per year
- ~1200 deaths annually in the US per year
- 10% of all lymphomas and 0.6% of all cancers
- Bimodal distribution (20, 65)
- HIV, prior solid organ or hematopoietic cell transplantation, and autoimmune diseases are at higher risk


Signs and Symptoms

- Painless LAD
- 50% mediastinal mass
- Dyspnea/cough/SVC syndrome
- 25% have B sx (fever/night sweats/wt loss)
- Pruritis
- BM involvement <10% at diagnosis
Pathology

- Classical
  - Nodular sclerosis
  - Mixed cellularity
  - Lymphocyte rich
  - Lymphocyte depleted
  - CD 15 and CD 30 +
  - Lack of pan B and pan T antigens (CD 19, 20, 79a, 3, and 7)

- Nodular lymphocyte predominant (5%)
  - CD 20 +

Reed-Sternberg (RS) cells in a reactive infiltrate (0.1 to 10%)

Prognostic Factors

• Ann Arbor Staging
• B Sx
• Early Stage (I-II, OS 90%)
• Favorable vs. Unfavorable
  – GHSG: ≥ 3 nodal areas, bulky mediastinum, ESR ≥ 50, extranodal disease.
  – EORTC: age ≥ 50, mediastinal bulk, ESR ≥ 50, ≥ 4 nodal sites
  – ECOG/NCI: Bulky disease, B sx
Prognostic Factors

- Advanced stage (III-IV, OS 60-90%)
- Hasenclever score
  - Age ≥ 45
  - Male
  - Albumin ≤ 4.0
  - Hb ≤ 10.5
  - Stage IV
  - WBC ≥ 15
  - Lymphopenia ≤ 0.6

<table>
<thead>
<tr>
<th>Hasenclever Score</th>
<th>5 yr FFP</th>
<th>5 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84%</td>
<td>89%</td>
</tr>
<tr>
<td>1</td>
<td>77%</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>67%</td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td>60%</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>51%</td>
<td>61%</td>
</tr>
<tr>
<td>≥ 5</td>
<td>42%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Early Favorable (I-II)

- 1990’s, STNI alone (subtotal nodal irradiation)
  - Cervical, axillary, mediastinal, hilar, para-aortic nodes, and spleen. 10 yr RFS ~80%

- Combined modality therapy (CMT)
  - 4 ABVD + 36 Gy IFRT

- GHSG H10
  - 2 or 4 cycles of ABVD, 20 or 30 Gy IFRT
  - 2 cycles of ABVD + 20 Gy IFRT
  - 5 yr EFS 91% and OS 93%
Early Unfavorable

- **GHSG HD11**
  - 4 ABVD vs. 4 BEACOPP + 20 Gy vs. 30 Gy IFRT.
  - 4 BEACOPP + 20 Gy and 4 ABVD + 30 Gy both superior to 4 ABVD + 20 Gy IFRT.
  - 5 yr OS 95%, 5 yr FFDP 85%

- **US and UK** tend to treat pts with B sx as advanced stage disease (6 ABVD)

- **Bulky disease, XRT** is still used

- **BCCA (Savage et al)**
  - ASH abstract 2015 showing 6 ABVD is acceptable in patients with bulky disease (PET neg)
Initial treatment: ABVD x 3

Stage IA, (33%), stage IIA, (67%)
63% favorable by EORTC criteria
68% favorable by GHSG criteria

PET +
4th cycle ABVD then IFRT

PET -
Randomization

30 Gy IFRT
No further treatment
PFS in the randomized PET –

3 year PFS: \( 94.5\% \) (91.3\%, 97.7\%) vs 90.8\% (86.8\%, 94.7\%)

HR 1.51 in favor of IFRT, \( p = 0.23 \)
OS in the randomized PET -

3 yr OS 97.1% (94.8%, 99.4%) vs 99.5% (98.6%, 100%)

HR 0.15 in favor of NFT, p = 0.07
Conclusions

- PET -, ABVD x 3
  - 3 yr PFS of 90.8% and OS of 99.5% in NFT
- PET -, ABVD x 3 + XRT
  - 3 yr PFS of 94.5% and OS of 97.1% with XRT
- PET +, ABVD x 4 + XRT
  - 3 yrs PFS 87.6%.
- PET can select a subgroup of patients who will do well with 3 cycles of ABVD
- Longer follow up is needed to establish in the impact of PET directed approach for 10 and 20 year survival data.
Initial Results of US Intergroup Trial of Response-Adapted Chemotherapy or Chemotherapy/Radiation therapy based on PET for Non-Bulky Stage I and II Hodgkin Lymphoma (HL) (CALGB/Alliance 50604)

David J. Straus, MD; Brandelyn Pitcher, MS; Lale Kostakoglu, MD; John C. Grecula, MD; Eric D. Hsi., MD; Heiko Schöder, MD; Sin-Ho Jung, PhD; Leslie L. Popplewell, MD; Julie E. Chang, MD; Craig H. Moskowitz, MD; Nina Wagner-Johnson, MD; John P. Leonard, MD; Jonathan W. Friedberg, MD; Brad S. Kahl, MD; Bruce D. Cheson, MD; Nancy L. Bartlett, MD

ASH 57th Annual Meeting
Abstract #578
• Phase II trial in newly-diagnosed stages I/II non-bulky HL conducted in Intergroup (CALGB/Alliance, SWOG, ECOG)
  – Favorable (17%)
  – Unfavorable (75%)
  – Unknown (7%)
Progression Free Survival

Follow-up time
Median: 2.1 years
Range: < 1 month – 4.3 years
1 Death (Suicide – PET +)

Est. 3-yr PFS
PET - 92% (84%-96%)
PET + 66% (32%-86%)

Hazard Ratio
PET - 92% (84%-96%)
PET + 66% (32%-86%)

Probability progression free
0 1 2 3 4
0.0 0.2 0.4 0.6 0.8
PET-negative
PET-positive
N= 131
N= 13
Events= 8
Events= 4
p-value= 0.0008

Follow-up time
Median: 2.1 years
Range: < 1 month – 4.3 years
1 Death (Suicide – PET +)

Est. 3-yr PFS
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Hazard Ratio
PET - 92% (84%-96%)
PET + 66% (32%-86%)
Conclusions

• PET/CT after 2 ABVD identified 91% PET negative
• Pts treated with 4 ABVD with estimated 3-yr PFS = 92%
• Pts by Deauville scores 1-3 (91%) rather than Deauville scores 1-2 (75%) (as in RAPID trial\(^1\)) maintains PFS >90% while reducing number of pts receiving IFRT
• Treating post 2 ABVD PET+ pts (9%) with escalated BEACOPP + IFRT may not result in clinically important improved PFS
• New approaches (antibody-drug conjugates and immune check point inhibitors - not chemotherapy) could be tested for post 2 ABVD PET+ pts
• Designing a trial with MDACC (ABVD + nivolumab) for PET+ patients
Advanced HL (III-IV)

- MOPP (nitrogen mustard, vinblastine, prednisone, and procarbazine)
- ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) vs. MOPP/ABV hybrid
  - 5 yr FFS 63% vs. 66%, 5 yr OS 82% vs. 81%
  - More death, toxicity, and secondary malignancy
- Stanford V
  - 12 week chemotherapy + XRT to sites of bulky disease (5 cm) and spleen.
  - Doxorubicin, vinblastine, mechloretamine, etoposide, vincristine, bleomycin, and prednisone
  - No difference in FFS or OS. (5 yr FFS 73% vs. 71%)
- BEACOPP/eBEACOPP
  - Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
  - Increased hem/inf toxicities, gonadal failure, MDS/AML (1.5% vs. 0.3%)
  - NRM 7% across all arms
  - PFS improved vs. ABVD, but OS same.
PET adapted therapy

- **Italian/Danish Study (Gallamini)**
  - 260 pts, newly diagnosed advanced HD. 6 ABVD, PET after 2 cycles.
  - 2 yr PFS 12.8% for PET +, 95% for PET neg pts

- **GITIL (Gallamini)**
  - PET + after 2 ABVD changed to BEACOPP, 2 year PFS 65%.

- **SWOG S0816**
  - ABVD x 2 cycles
  - If PET Positive, change to esc BEACOPP x 6 cycles
  - If PET negative, ABVD x 4 more cycles.
A Phase II US Intergroup Trial of Response-Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging (SWOG S0816): Preliminary Results


Register → ABVD x 2

PET- → ABVD x 4

PET+ → BEACOPP_{escalated} x 6
S0816 PFS by PET2 Result

Arm 1: Continued ABVD

Arm 2: eBEACOPP

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Failed</th>
<th>2-Year Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET negative</td>
<td>277</td>
<td>39</td>
</tr>
<tr>
<td>PET positive</td>
<td>55</td>
<td>16</td>
</tr>
</tbody>
</table>
Advanced HL

1. Early results suggest a possible improvement in PFS for PET2+ patients switched to eBEACOPP compared to historical experience with continued ABVD.

2. Longer follow-up of S0816 is necessary.

3. Echelon 1 trial (AVD + brentuximab vedotin vs. ABVD)

4. Collaborating with MSK (ABVD + brentuximab vedotin for PET + patients)
Relapsed/Refractory HL

- 20%-30% of Hodgkin lymphoma (HL) patients are refractory/relapsed to induction regimen of ABVD
- Standard combination chemotherapy regimens followed by AHCT can cure ~50% of patients.
- CR status at AHCT is predictive of outcome. (2 year PFS 75% vs. 31%)

<table>
<thead>
<tr>
<th>Salvage regimen</th>
<th>RR (%)</th>
<th>CR (%) (no PET)</th>
<th>CR by PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE</td>
<td>88%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>DHAP</td>
<td>87%</td>
<td>21%</td>
<td>60%</td>
</tr>
<tr>
<td>GVD</td>
<td>70%</td>
<td>19%</td>
<td>Aug ICE 60%</td>
</tr>
<tr>
<td>GDP</td>
<td>62%</td>
<td>9%</td>
<td>IGEV 53.8%</td>
</tr>
</tbody>
</table>

Moskowitz CH et al. Blood. 2001
Santoro A et al. Haematologica 2007
Kuruvilla J et al. Cancer
Moskowitz A et al. Blood 2010
Brentuximab Vedotin antibody-drug conjugate (ADC)

- Monomethyl auristatin E (MMAE), microtubule-disrupting agent
- Protease-cleavable linker
- Anti-CD30 monoclonal antibody

1. Brentuximab vedotin binds to CD30
2. Brentuximab vedotin-CD30 complex is internalized and traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

© 2014 Seattle Genetics, Inc.
• BV given at 1.8 mg/kg IV outpatient every 3 weeks for 4 cycles max
• No premedication with first cycle
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%) or Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>34 (11-67)</td>
</tr>
<tr>
<td><strong>Institution</strong></td>
<td></td>
</tr>
<tr>
<td>City of Hope</td>
<td>31 (84%)</td>
</tr>
<tr>
<td>Weill Cornell</td>
<td>6 (16%)</td>
</tr>
<tr>
<td><strong>Stage at Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>19 (51%)</td>
</tr>
<tr>
<td>III-IV</td>
<td>18 (49%)</td>
</tr>
<tr>
<td><strong>B symptoms</strong></td>
<td>23 (62%)</td>
</tr>
<tr>
<td><strong>Bulky Disease (&gt; 5 cm)</strong></td>
<td>32 (86%)</td>
</tr>
<tr>
<td><strong>Induction Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>ABVD</td>
<td>34</td>
</tr>
<tr>
<td>ABVD/BEACOPP</td>
<td>2</td>
</tr>
<tr>
<td>ABVE-PC</td>
<td>1</td>
</tr>
<tr>
<td><strong>Prior XRT</strong></td>
<td>9 (24%)</td>
</tr>
<tr>
<td><strong>Best Response to Induction</strong></td>
<td></td>
</tr>
<tr>
<td>Primary Refractory</td>
<td>24 (65%)</td>
</tr>
<tr>
<td>Relapsed (within 7 months)</td>
<td>13 (35%)</td>
</tr>
</tbody>
</table>
### Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Best response to BV, N=37</th>
<th>Response to combination chemotherapy (ICE/DICE/IGEV/GND) post-BV, N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>25/37 (68%)</td>
<td>16/18 (89%)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>13/37 (35%)</td>
<td>10/18 (56%)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>12/37 (32%)</td>
<td>6/18 (33%)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>10/37 (27%)</td>
<td>1/18 (6%)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>2/37 (5%)</td>
<td>1/18 (6%)</td>
</tr>
</tbody>
</table>

Univariate analysis: no differences in terms of age, sex, disease stage, response to induction, bulky disease, or B symptoms.
# AHCT Results

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N or Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Types of HCT</strong></td>
<td></td>
</tr>
<tr>
<td>- AHCT</td>
<td>32 (86%)</td>
</tr>
<tr>
<td>- AlloHCT</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>- No HCT</td>
<td>3 (8%)</td>
</tr>
<tr>
<td><strong>Disease Status at AHCT</strong></td>
<td></td>
</tr>
<tr>
<td>- CR</td>
<td>23/32 (72%)</td>
</tr>
<tr>
<td>- PR</td>
<td>8/32 (25%)</td>
</tr>
<tr>
<td>- SD</td>
<td>1/32 (3%)</td>
</tr>
<tr>
<td><strong>Salvage regimen</strong></td>
<td></td>
</tr>
<tr>
<td>- BV only</td>
<td>15/32 (47%)</td>
</tr>
<tr>
<td>- BV followed by chemotherapy</td>
<td>16/32 (50%)</td>
</tr>
<tr>
<td>- BV followed by radiation</td>
<td>1/32 (3%)</td>
</tr>
</tbody>
</table>
COH Patients

Cumulative Incidence / Survival Probability

Time (Months) from Transplant

Overall Survival
- Progression Free Survival
- Non-Relapse Mortality

<table>
<thead>
<tr>
<th>COH patients (25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median f/u</td>
</tr>
<tr>
<td>OS</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>PFS</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
COH Patients

CR vs. Non-CR

Disease Status at HCT
- CR (n=17)
- > CR (n=8)

Survival Probability

Time (months) from Date of Transplant

CR: 76.5% (48.8, 90.4)
non CR: 50.0% (15.2, 77.5)
P=0.047
COH Patients-PFS

BV vs. BV + Chemo

2nd Salvage Therapy

- BV only (n=13)
- BV + Chemo (n=11)

BV: 84.6% (51.2, 95.9)
BV + Chemo: 54.5% (22.9, 78.0)
P=0.036
Summary/Conclusion

- BV as first line post induction has ORR 68%, CR 35%
- Among AHCT patients, 23/32 (72%) were transplanted in CR, and 15/32 (47%) received BV only
- Patients transplanted in CR had better outcomes
- Patients transplanted with BV only also had good outcomes post AHCT
- For patients with relapsed/refractory HL after induction chemotherapy, BV can be considered as first line salvage therapy (CR)
- Current study combines BV + nivolumab in this setting
Post AutoHCT

• AHERA
  – Randomized phase III trial post AHCT placebo vs. BV in high risk HL
  – Median PFS 15.8 month compared to not reached
  – 3 year PFS 61% vs. 43% in placebo
  – The PFS plateau remains and clearly separates out.

• Phase II study using pembrolizumab for consolidation after autoHCT
Novel Drugs

- Brentuximab Vedotin
  - Anti CD 30 ADC. ORR 73%, CR 33%
- Lenalidomide
  - IMID, ORR 19%
- Everolimus
  - mTOR inhibitor, ORR ~40%
- Bendamustine
  - Alkylating agent, ORR ~40%
- PD-1 inhibitors
  - Nivolumab, ORR 87%, CR 17%.
  - Pembrolizumab, ORR 66%, CR 21%.
  - Avelumab
- PI3 inhibitors
The PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- Binding of PD-1 to PD-L1 or PD-L2 leads to downregulation of T-cell function
- This mechanism is usurped by many tumors
- PD-1 blockade through mAb therapy can restore effective anti-tumor immunity

### Pembrolizumab

<table>
<thead>
<tr>
<th></th>
<th>Transplant Failure N = 22</th>
<th>Transplant Ineligible/Refused N = 9</th>
<th>Total N = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td>16 (73%)</td>
<td>4 (44%)</td>
<td>20 (65%)</td>
</tr>
<tr>
<td><strong>Complete Remission</strong></td>
<td>3 (14%)</td>
<td>2 (22%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td><strong>Partial Remission</strong></td>
<td>13 (59%)</td>
<td>2 (22%)</td>
<td>15 (48%)</td>
</tr>
<tr>
<td><strong>Stable Disease</strong></td>
<td>4 (18%)</td>
<td>3 (33%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td><strong>Progressive Disease</strong></td>
<td>2 (9%)</td>
<td>2 (22%)</td>
<td>4 (13%)</td>
</tr>
</tbody>
</table>

Armand et al. ASH 2015
### Safety

#### Treatment-Related AEs Any Grade in ≥ 3 Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Related AE</td>
<td>21 (68)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>11 (36)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (13)</td>
</tr>
<tr>
<td>General</td>
<td>9 (29)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Investigations</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Skin</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

Armand et al, ASH 2015
## Nivolumab

<table>
<thead>
<tr>
<th>Best Objective Response</th>
<th>cHL (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>20 (87)</td>
</tr>
<tr>
<td>CR</td>
<td>5 (22)</td>
</tr>
<tr>
<td>PR</td>
<td>15 (65)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (13)</td>
</tr>
</tbody>
</table>

Ansell et al. ASH 2015
Select Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>cHL (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade, n (%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Colitis</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1 (4)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1 (4)</td>
</tr>
<tr>
<td>AST increased</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Skin</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Pruritic rash</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Skin hypopigmentation</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Hypersensitivity/infusion reaction</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

- All AEs were Grade 1/2 except colitis and pneumonitis which were Grade 3
Allo-HCT

• Approximately 50% of patients with Hodgkin lymphoma relapse after AHCT
• Median OS in post-transplant relapse is only 2.4 years (Horning et al. 2008)
• Myeloablative (TRM ~40%) vs. RIC (TRM~15%)
• A minority of patients are eligible
• Acute graft-vs-host disease (GVHD) in ≈50% of patients
• Chronic GVHD in ≈35% of patients
• High relapse rate: 5-year PFS ≈20%
## Allo-HCT

<table>
<thead>
<tr>
<th>Group</th>
<th>Conditioning Regimen</th>
<th>Cell Source</th>
<th>Follow-up</th>
<th>NRM</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBMT</td>
<td>BEAM Flu/TBI Flu/Mel Bu/Mel/Cy</td>
<td>PB BM</td>
<td>75 months</td>
<td>3 yr, 24%</td>
<td>5 yr, 28%</td>
<td>5 yr, 18%</td>
</tr>
<tr>
<td>Fred Hutchinson</td>
<td>TBI Flu/TBI</td>
<td>PB</td>
<td>25 months</td>
<td>MRD: 2 yr, 21% MUD: 2 yr, 8%</td>
<td>MRD: 2 yr, 53% MUD: 2 yr, 58%</td>
<td>MRD: 2 yr, 23% MUD: 2 yr, 29%</td>
</tr>
<tr>
<td>Dana Farber</td>
<td>Bu/Flu</td>
<td>PB BM</td>
<td>26 months</td>
<td>3 yr, 23%</td>
<td>3 yr, 56%</td>
<td>3 yr, 22%</td>
</tr>
<tr>
<td>MDACC</td>
<td>Flu/Mel</td>
<td>PB BM</td>
<td>24 months</td>
<td>2 yr, 15%</td>
<td>2 yr, 64%</td>
<td>2 yr, 32%</td>
</tr>
<tr>
<td>COH</td>
<td>Flu/Mel</td>
<td>PB UCD</td>
<td>26 months</td>
<td>2 yr, 13%</td>
<td>2 yr, 60%</td>
<td>2 yr, 27%</td>
</tr>
</tbody>
</table>

Chen et al.  Am J Hem 2010
Brentuximab Vedotin (SGN-35) Enables Successful Reduced Intensity Allogeneic Hematopoietic Cell Transplantation in Relapsed/Refractory Hodgkin Lymphoma

Robert Chen, MD, Stephen J. Forman, MD, Joycelynne Palmer, PhD, Ni-Chun Tsai, MS, Leslie Popplewell, MD, Maria Delioukina, MD, Alejandra Torres, MS, Bernie Pulone, RN, Eileen Smith, MD, Chatchada Karanes, MD, Auayporn Nademanee, MD, Len Farol, MD, Samer Khaled, MD, Paul O'Donnell, MD, PhD, David Maloney, MD, PhD, Schickwann Tsai, MD, Laurie E. Grove, PA-C, Ajay K. Gopal MD.

City of Hope National Medical Center, SCCA/Fred Hutchinson Cancer Research Center, and Seattle Genetics, Inc.

Lymphoma SPORE, COH Comprehensive Cancer Center Grant
RC is a Tim Nesvig Lymphoma Fellow and K12 recipient
AG is a Clinical Research Scholar of the Leukemia and Lymphoma Society
Results:

- CR 100%
- 1-year OS: 100%
- 1-year PFS: 92.3% (CI: 61.3, 98.7)
- 1-year Relapse Rate: 7.7% (CI: 1.3, 38.7)
- 1-year NRM: 0%
Treatment Guidelines

Limited Stage Favorable
- ABVD x 2 + 20 cGY XRT
- Restage PET
  - PET negative: ABVD x 2
    (total ABVD x 4)
  - PET positive: ABVD x 4 + 30 cGY XRT

Limited Stage Unfavorable
- ABVD x 4 + 30 cGY XRT

Advanced Stage
- ABVD x 6
Relapsed Refractory to induction

1) Clinical Trial
2) Brentuximab vedotin based salvage chemotherapy
3) ICE chemotherapy

If CR/PR then autoHCT, if SD/PD then
1) Clinical trial
2) Gemcitabine based salvage
3) Allo-HCT
HL Clinical Trials at COH

• Current
  – A Phase 1/2 Study Evaluating Brentuximab Vedotin in Combination with Nivolumab after Failure of Frontline Therapy (Dr. Alex Herrera)
  – A Phase 1 PK/PD Study Of Avelumab (MSB0010718C) In Patients With Previously Treated Advanced Stage Classical Hodgkin's Lymphoma
  – A Phase 1a/1b Dose Escalation and Expansion Trial of Single-agent TTI-621, a Novel Biologic Targeting CD47, in Subjects with Relapsed or Refractory Hematologic Malignancies
  – Maintenance trial of pembrolizumab post AHCT (Dr. Alex Herrera)
  – ATAC-BEAM conditioning regimen for AHCT (Dr. Eileen Smith)

• Opening Soon
  – COH lead Phase II Trial of Ibrutinib Plus Brentuximab Vedotin in Relapsed/Refractory Hodgkin Lymphoma
  – A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma
  – AVD + brentuximab vedotin + XRT for bulky early stage disease.

• Designing phase
  – Limited stage (ABVD + nivolumab) for PET 2+
  – Advanced stage (ABVD + nivolumab ) for PET 2 –
  – Consolidation with Brentuximab vedotin plus nivolumab post AHCT.