Hodgkin Lymphoma:

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2/05/15

City of Hope National Medical Center
Disclosures

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 II Hodgkin lymphoma.
Background

• 9000 new cases in the US per year
• 1200 death 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/NS/wt loss)
- Pruritis, alcohol related pain
- BM involvement <10% at diagnosis
Pathology

- Reed-Sternberg (RS) cells in a reactive infiltrate
- Only make up 0.1 to 10% of cells in the tumor
- 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 +
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: Bulk 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>Score</th>
<th>5 yr FFP</th>
<th>5 yr OS</th>
</tr>
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<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

- EORTC changed to 20 Gy IFRT

- GHSG H10
  - 2 or 4 cycles of ABVD, 20 or 30 Gy IFRT
  - 2 cycles of ABVD + 20 Gy IFRT best
  - 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)

• If bulky disease, XRT is still used
Initial treatment: ABVD x 3

Re-assessment: PET scan performed

**PET +**

4th cycle ABVD then IFRT

**PET -**

Randomisation

- 30 Gy IFRT
- No further treatment
Demographics

- 602 patients with newly diagnosed 2003-2010
- 321 male, 281 female
- Median age of 34 years
- Stage IA, 139 (33%), stage IIA, 281 (67%)
- 63% favourable by EORTC criteria, 68% favourable by GHSG criteria
PFS in the randomised PET –

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

HR 1.51 in favour of IFRT, p=0.23

ITT, n=420

Graph showing survival rates over time.
3 yr OS 97.1% (94.8%, 99.4%) vs 99.5% (98.6%, 100%)

HR 0.15 in favour of NFT, p = 0.07
Conclusions

• PET -, 3 yr PFS of 90.8% and OS of 99.5% in NFT
• PET -, 3 yr PFS of 94.5% and OS of 97.1% with XRT
• PET +, 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
CALGB 50604 Design

- Phase II trial in newly-diagnosed stages I/II non-bulky HL conducted in Intergroup (CALGB/Alliance, SWOG, ECOG)

Prophylactic G-CSF only after febrile neutropenia or neutropenia and infection with ABVD. Prophylactic G-CSF with escalated BEACOPP.
### CALGB 50604

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>31</td>
</tr>
<tr>
<td>(18-58)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>88 (54%)</td>
</tr>
<tr>
<td>Female</td>
<td>76 (46%)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>17 (10%)</td>
</tr>
<tr>
<td>IB</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>IIA</td>
<td>90 (55%)</td>
</tr>
<tr>
<td>IIB</td>
<td>37 (23%)</td>
</tr>
<tr>
<td>IIAE</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>IIBE</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Unknown/Not reported</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>Total stage B</td>
<td>42 (26%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
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<tbody>
<tr>
<td><strong>Performance Score</strong></td>
<td></td>
</tr>
<tr>
<td>ECOG = 0</td>
<td>119 (73%)</td>
</tr>
<tr>
<td>ECOG = 1</td>
<td>35 (21%)</td>
</tr>
<tr>
<td>Unknown/Not reported</td>
<td>10 (6%)</td>
</tr>
<tr>
<td><strong>ESR</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>106 (65%)</td>
</tr>
<tr>
<td>50 +</td>
<td>40 (24%)</td>
</tr>
<tr>
<td>Unknown/Not reported</td>
<td>18 (11%)</td>
</tr>
<tr>
<td><strong>Number of Sites</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 3</td>
<td>43 (26%)</td>
</tr>
<tr>
<td>3 +</td>
<td>112 (68%)</td>
</tr>
<tr>
<td>Unknown/Not reported</td>
<td>9 (5%)</td>
</tr>
<tr>
<td><strong>German Hodgkin Study Group Classification</strong></td>
<td></td>
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<tr>
<td>Early Stage Favorable</td>
<td>28 (17%)</td>
</tr>
<tr>
<td>Early Stage Unfavorable</td>
<td>123 (75%)</td>
</tr>
<tr>
<td>Advanced Stage</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (7%)</td>
</tr>
</tbody>
</table>
CALGB 50604 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
6.04 (1.82-20.08)
Conclusions

- PET/CT after 2 ABVD identified 91% PET- pts treated with 4 ABVD with estimated 3-yr PFS = 92%
- Defining post 2 ABVD PET- 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 IF RT
- Treating post 2 ABVD PET+ pts (9%) with escalated BEACOPP + IF RT 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

\(^1\)NEJM 372: 1598-1607, 2015
Advanced Stage (III-IV)

- MOPP (nitrogen mustard, vinblastine, prednisone, and procarbazine)
- MOPP/ABVD to ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine)
  - 856 pts, CR 76% vs 80%
  - 5 yr FFS 63% vs. 66%
  - 5 yr OS 82% vs. 81%
  - More death, toxicity, and secondary malignancy in MOPP/ABV
Stanford V

• Stanford V
  – 12 week chemotherapy + XRT to sites of bulky disease (5 cm) and spleen.
  – Doxorubicin, vinblastin, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone

• Italian Study Stanford V vs. ABVD
  – 5 yr OS superior for ABVD
  – Less XRT (66% vs. 91% in original paper)

• North American intergroup trial Stanford V vs. ABVD
  – 854 pts over 7 years.
  – The 5 year FFS 73% ABVD vs. 71% Stanford V.
  – No difference in FFS or OS.
Advanced Hodgkin

• BEACOPP
  – bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
  – GHSG HD 9, 1195 pts
    • COPP/ABVD vs. BEACOPP vs. esc BEACOPP
    • Esc BEACOPP reduce early progression and increased OS when compared with COPP-ABVD
    • Increased hem/inf toxicities, gonadal failure, MDS/AML (1.5% vs. 0.3%)
    • NRM 7% across all arms
  – GISL HD 2000
    • ABVD vs. BEACOPP (4 esc and 2 reg).
    • OS same, BEACOPP better than ABVD in PFS.
    • But increased hem/inf toxicities.
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.

- **GHSG HD**
  - 2 x Esc BEACOPP, if PET negative, 4 vs. 6 more of esc BEACOPP.
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


For SWOG, CALGB/Alliance, ECOG, and AMC
Schema for HIV-negative patients

Register → ABVD x 2

PET- → ABVD x 4

PET+ → BEACOPP_{escalated} x 6

Schema for HIV-positive patients

Register → ABVD x 2

PET- → ABVD x 4

PET+ → BEACOPP_{baseline} x 6
S0816: Preliminary Outcome Results
(Response Rates in HIV-negative patients)

- **Arm 1: ABVD**
  - 96%

- **Arm 2: eBEACOPP**
  - 49% (42% PR, 49% CR)
S0816 PFS by PET2 Result

<table>
<thead>
<tr>
<th></th>
<th>Patients at Risk</th>
<th>Failed</th>
<th>2-Year Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: Continued ABVD</td>
<td>277</td>
<td>39</td>
<td>79% (95% CI: 72-85%)</td>
</tr>
<tr>
<td>Arm 2: eBEACOPP</td>
<td>55</td>
<td>16</td>
<td>61% (95% CI: 44-74%)</td>
</tr>
</tbody>
</table>

PET negative

PET positive
1. Response-adapted therapy with centralized interim PET review is highly feasible in a US cooperative intergroup setting.

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

3. Results of randomized studies of the value of interim PET imaging are eagerly awaited.

4. Molecular biomarker studies may define the PET2-patients destined to relapse, allowing implementation of novel therapies in the future.

5. Longer follow-up of S0816 is necessary.
• Safety of De-escalation and Efficacy of Escalation in the International RATHL Study (CRUK/07/033)


• PET – after 2 cycles, randomize to ABVD x 4 vs. AVD x 4
PET -, PFS and OS
• After a negative interim FDG-PET scan it is safe to omit bleomycin from subsequent cycles, without consolidation radiotherapy
• Omission of bleomycin reduces toxicity, especially dyspnoea, thromboembolism and neutropenic fever
Randomized, Open-label, Phase 3 Trial of A + AVD Versus ABVD as Frontline Therapy in Patients with Advanced Classical Hodgkin Lymphoma

- Untreated stage III and IV HL
- ABVD or AVD + BV
- Primary endpoint is 3 year PFS (ABVD 75%, and AVD + BV 82.5%)
- 1040 pts
Lymphocyte Predominant Disease

- ~5% of all Hodgkin lymphoma
- LH (Lymphohistiocytic)
- CD 20 positive, CD 30, 15 negative
- XRT
- ABVD
- CHOP
- Rituximab
- R-CVP, R-CHOP
- R-ABVD
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></td>
</tr>
<tr>
<td>GVD</td>
<td>70%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>GDP</td>
<td>62%</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

Josting A et al. *Ann Oncol.* 2005  
Santoro A et al. *Haematologica* 2007  
Kuruvilla J et al. *Cancer*  
Moskowitz A et al. *Blood* 2010  
Brentuximab Vedotin

- A phase II pivotal trial demonstrated 75% ORR, with 34% CR, and a favorable toxicity profile in HL patients
- We report the post AHCT outcomes of a phase II trial evaluating BV as first line salvage therapy in relapsed or refractory HL prior to AHCT
• 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>
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<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>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>
</tr>
<tr>
<td></td>
<td>16/18 (89%)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>13/37 (35%)</td>
</tr>
<tr>
<td></td>
<td>10/18 (56%)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>12/37 (32%)</td>
</tr>
<tr>
<td></td>
<td>6/18 (33%)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>10/37 (27%)</td>
</tr>
<tr>
<td></td>
<td>1/18 (6%)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>2/37 (5%)</td>
</tr>
<tr>
<td></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>
<tr>
<td><strong>AHCT centers</strong></td>
<td></td>
</tr>
<tr>
<td>-COH</td>
<td>25/32 (78%)</td>
</tr>
<tr>
<td>-Cornell</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>-UCLA</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>-UCSD</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
# AHCT Outcomes

<table>
<thead>
<tr>
<th></th>
<th>All patients (32)</th>
<th>COH patients (25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median f/u</strong></td>
<td>20.9 months (10.1, 41.1)</td>
<td>24.2 months (10.1, 39.6)</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>18 months -96.9% (79.8, 99.6)</td>
<td>2 yrs -89.1% (61.5, 97.3)</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>18 months -71.9% (52.9, 84.3)</td>
<td>2 yrs -68.0% (46.1, 82.5)</td>
</tr>
<tr>
<td><strong>NRM D100</strong></td>
<td>-3.1% (0.5, 21.5)</td>
<td>-4% (0,6, 27.3)</td>
</tr>
</tbody>
</table>
COH Patients

OS/PFS/NRM

- Overall Survival
- Progression Free Survival
- Non-Relapse Mortality

Cumulative Incidence / Survival Probability

Time (Months) from Transplant

[Graph showing cumulative incidence/survival probability over time]
COH Patients

CR vs. Non-CR

Disease Status at HCT
- CR (n=17) - 76.5% (48.8, 90.4)
- non CR (n=8) - 50.0% (15.2, 77.5)
P=0.047

Survival Probability

Time (months) from Date of Transplant
COH Patients - PFS

BV vs. BV + Chemo

Survival Probability

Time (months) from Date of Transplant

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%
• 32/37 (86%) went to AHCT, 2 went to allo-HCT, 3 not salvaged
• Among AHCT patients, 23/32 (72%) were transplanted in CR, and 15/32 (47%) received BV only
• Stem cell mobilization, engraftment, and peri-transplant toxicities not adversely affected
• 18 months (all) and 2 year (COH) PFS/OS/NRM are consistent with historical controls
• Patients transplanted in CR had better outcomes
• Patients transplanted with BV only also had good outcomes post AHCT
• Results of this study are similar to Moskowitz A et al (Lancet 2015)
• For patients with relapsed/refractory HL after induction chemotherapy, BV can be considered as first line salvage therapy (CR)
• Future studies aim to combine BV + novel agents in this setting
Novel Drugs

- **Brentuximab Vedotin**
  - Anti CD 30 ADC. ORR 73%, CR 33%
- **PD-1 inhibitors**
  - Nivolumab, ORR 87%, CR 17%.
  - Pembrolizumab, ORR 66%, CR 21%.
  - Avelumab
- **Lenalidomide**
  - IMID, ORR 19%
- **Everolimus**
  - mTOR inhibitor, ORR ~40%
- **Bendamustine**
  - Alkylating agent, ORR ~40%
- **PI3 inhibitors**
PD-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure: Safety, Efficacy, and Biomarker Assessment

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The PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- Binding of PD-1 by its ligands 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 is a humanized anti-PD1 mAb with activity in several solid tumors

## Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Brentuximab Failure</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Transplant Failure</td>
<td>Transplant Ineligible/Refused</td>
<td>Total N = 31</td>
<td></td>
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<tr>
<td></td>
<td>N = 22</td>
<td>N = 9</td>
<td></td>
<td></td>
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<tr>
<td>Overall Response Rate</td>
<td>16 (73%)</td>
<td>4 (44%)</td>
<td>20 (65%)</td>
<td></td>
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<tr>
<td>Complete Remission</td>
<td>3 (14%)</td>
<td>2 (22%)</td>
<td>5 (16%)</td>
<td></td>
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<tr>
<td>Partial Remission</td>
<td>13 (59%)</td>
<td>2 (22%)</td>
<td>15 (48%)</td>
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<tr>
<td>Stable Disease</td>
<td>4 (18%)</td>
<td>3 (33%)</td>
<td>7 (23%)</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>2 (9%)</td>
<td>2 (22%)</td>
<td>4 (13%)</td>
<td></td>
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<tr>
<td>Treatment-Related AEs</td>
<td>n (%)</td>
<td></td>
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<td>------------------------------------------</td>
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<tr>
<td>Any Related AE</td>
<td>21 (68)</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal</td>
<td>11 (36)</td>
<td></td>
<td></td>
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<tr>
<td>Diarrhea</td>
<td>5 (16)</td>
<td></td>
<td></td>
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<tr>
<td>Nausea</td>
<td>4 (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>9 (29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>6 (19)</td>
<td></td>
<td></td>
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<tr>
<td>Hypothyroidism</td>
<td>5 (16)</td>
<td></td>
<td></td>
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<tr>
<td>Investigations</td>
<td>6 (19)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Metabolism and nutrition</td>
<td>5 (16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>5 (16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (10)</td>
<td></td>
<td></td>
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<tr>
<td>Skin</td>
<td>5 (16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>3 (10)</td>
<td></td>
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</table>
Summary and Conclusions

- Pembrolizumab is associated with an acceptable safety profile in cHL.
- Pembrolizumab has high anti-tumor activity with durable responses in heavily pre-treated patients with brentuximab failure.
  - ORR for entire HL cohort = 65%
  - ORR for transplant failure = 73%
  - ORR for transplant ineligible = 44%
  - 71% of subjects have a DOR ≥ 24 weeks
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 y, 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>
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%
Late Complications of Therapy

- Patients treated for HL before age 21:
  - Are nearly 14 times more likely than the general population to die from cardiovascular disease
  - Are nearly 15 times more likely to die from solid tumors

Mortality risk due to HL plateaus after 10 years, whereas risks due to second malignancy, cardiovascular disease and other causes increase continually following treatment.

Long Term Complication

- Secondary malignancies (solid organ and Leukemia/MDS/lymphoma)
- 18.5 times greater than general population
- Breast CA most common in female pt
- US recommends mammogram 10 years after treatment or at 40 yrs of age.
- Increased incidence of myocardial infarction, CHF, CAD. Most likely related to XRT and anthracycline containing therapy.
- Subfertility (~50% BEACOPP vs ~5% ABVD), endocrine dysfunction, peripheral neuropathy.