HOW I TREAT HODGKIN LYMPHOMA
UPDATE 2018

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Director, Matched Unrelated Donor Program
I do not have anything to disclose
In 2017, an estimated 8,260 people will be diagnosed with HL in the US

~1,070 deaths annually in the US per year

10% of all lymphomas and 0.6% of all cancers

Bimodal distribution, 15-30 and another peak in adult aged ≥ 55

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%)

## NCCN Guidelines Version 2.2013
### Hodgkin Lymphoma

### Examples of Unfavorable Risk Factors for Stage I-II Hodgkin Disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>GHSG</th>
<th>EORTC</th>
<th>NCIC</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥50</td>
<td>≥40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td>MC or LD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR and B symptoms</td>
<td>&gt;50 if A; &gt;30 if B</td>
<td>&gt;50 if A; &gt;30 if B</td>
<td>&gt;50 or any B sx</td>
<td>&gt;50 or any B sx</td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>MMR &gt; .33</td>
<td>MTR &gt; .35</td>
<td>MMR &gt; .33 or &gt; 10 cm</td>
<td>MMR &gt; .33</td>
</tr>
<tr>
<td>Nodal sites</td>
<td>&gt;2*</td>
<td>&gt;3**</td>
<td>&gt;3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>E lesion</td>
<td>any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulky</td>
<td></td>
<td></td>
<td>&gt;10 cm</td>
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</table>

GHSG = German Hodgkin Study Group  
EORTC = European Organization for the Research and Treatment of Cancer  
NCIC = National Cancer Institute, Canada

*MC = Mixed cellularity  
LD = Lymphocyte depleted  
MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter  
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

*The GHSG definition of nodal sites differs from the Ann Arbor System in that the infracavicular region is included with the ipsilateral cervical/supraclavicular, the bilateral hilar are included with the mediastinum, and the abdomen is divided into 2 regions, upper (spleen hilum, liver hilum, celiac) and lower.

**The EORTC definition of nodal sites differs from the Ann Arbor System in that the infracavicular region is included with the ipsilateral axilla and the bilateral hilar is included with the mediastinum.

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**International Prognostic Score (IPS)**  
1 point per factor (advanced disease)

- Albumin < 4 g/dL  
- Hemoglobin < 10.5 g/dL  
- Male  
- Age ≥45 years  
- Stage IV disease  
- Leukocytosis (white blood cell count at least 15,000/mm³)  
- Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm³)


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**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
International Prognostic Factors For Advanced Stage

- Advanced stage (III-IV, OS 60-90%)
- Hasenclever score
  - Age ≥ 45
  - Male
  - Albumin ≤ 4.0
  - Hb ≤ 10.5
  - Stage IV
  - WBC ≥ 15,000/mm³
  - Lymphopenia, ALC ≤ 600/mm³

<table>
<thead>
<tr>
<th>Score</th>
<th>5 yr FFP</th>
<th>5 yr OS</th>
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<tr>
<td>0</td>
<td>84%</td>
<td>89%</td>
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<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>
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</tbody>
</table>

Treatment of Early stage HL

- How many cycles of chemo?
- What dose of Radiation?
- Which RT field to use?
- Can Chemotherapy alone be used?
- What is the role of FDG PET?
Early Favorable (I-II)

• Radiation Alone was a standard treatment for many decades, however, with the increased risk of heart disease, pulmonary toxicity and second cancers, it is no longer recommended

• Combined modality therapy (Bonadonna et al)
  – 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 96%

• RAPID Trial
  • ABVD x 3 cycles if PET is negative after ABVDx3
  • 3yrs PFS 91%, OS 97%
Stage I-II Unfavorable

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

- Chemotherapy alone ABVD x 6 if PET negative (BCCA, EORTC H10 trial), although ABVD+INRT resulted in fewer progression

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

- Bulky disease, XRT is still used, although RT can be omitted if PET negative (BCCA)
HD11: Early unfavourable stage

Early unfavourable stage

- 4 x ABVD
  - 30 Gy IF
- 4 x ABVD
  - 20 Gy IF
- 4 x BEACOPP base
  - 30 Gy IF
- 4 x BEACOPP base
  - 20 Gy IF
HD11: FFTF according to chemotherapy

Pts. at Risk
4xABVD: 649, 584, 453, 301, 259, 168, 78
4xBEACOPP: 644, 585, 468, 300, 264, 183, 68

At 3 years
4xABVD: 87%
4xBEACOPP: 88%

95% KI: [84 ; 90]
95% KI: [85 ; 91]
HD11: FFTF according to radiotherapy

![Graph showing probability against time for different radiation doses.]

- **Pts. at Risk**
  - 30 Gy: 634, 591, 467, 296, 261, 177, 76
  - 20 Gy: 636, 578, 454, 305, 262, 174, 70

- **At 3 years**
  - 30 Gy: 90%
  - 20 Gy: 87%
  - 95% KI: [87; 92]
  - 95% KI: [84; 90]
Prognostic Value of FDG-PET for Treatment of Hodgkin Lymphoma
Deauville Criteria for Interpretation of Interim PET

- **Negative scan:**
  - Score 1: No uptake
  - Score 2: Uptake ≤ mediastinum

- **Positive scan**
  - Score 3: Uptake > mediastinum but ≤ liver
  - Score 4: Uptake > liver at any site
  - Score 5: Uptake >> liver ± new sites
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
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
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
Study Overview and Conclusion

• Among patients with early-stage Hodgkin's lymphoma who have negative PET findings after three cycles of chemotherapy, radiotherapy produces a 3.8-percentage-point improvement in 3-year progression-free survival.

• However, 90% of patients are cured by chemotherapy alone.

• The results of this study did not show the noninferiority of the strategy of no further treatment after chemotherapy with regard to progression-free survival.

• Patients with early-stage Hodgkin’s lymphoma and negative PET findings after three cycles of ABVD had a very good prognosis either with or without consolidation radiotherapy.
Fig 1. Study design. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPPesc, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; F, favorable; INRT, involved-node radiotherapy; PET, positron emission tomography; U, unfavorable.

Published in: Marc P.E. André; Théodore Girinsky; Massimo Federico; Oumédaly Reman; Catherine Fortpied; Manuel Gotti; Olivier Casasnovas; Pauline Brice; Richard van der Maazen; Alessandro Re; Véronique Edeline; Christophe Fermé; Gustaaf van Imhoff; Francesco Merli; Réda Bouabdallah; Catherine Sebban; Lena Specht; Aspasia Stamatoullas; Richard Delarue; Valeria Fiaccadori; Monica Bellei; Tiana Raveloarivahy; Annibale Versari; Martin Hutchings; Michel Meignan; John Raemaekers; JCO 2017, 35, 1786-1794.
DOI: 10.1200/JCO.2016.68.6394
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PFS in Early Stage HL with Early Negative PET

A
Progression-free survival (%)

Favorable
ABVD x4

B
Progression-free survival (%)

Unfavorable
ABVD x 6
Fig 3. Progression-free and overall survival of early positron emission tomography (PET)–positive patients. Shown are the rates of (A) progression-free and (B) overall survival of early PET-positive patients who were randomly assigned to treatment with either standard doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) + involved-node radiotherapy (INRT; n = 192) or experimental bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc) + INRT (n = 169). HR, hazard ratio, O observed; n, number of patients.

Published in: Marc P.E. André; Théodore, et al.; *JCO* 2017, 35, 1786-1794.
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)
  – 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
6.04 (1.82-20.08)
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) 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
**Future Trials**

- **ES Favorable and Unfavorable**
  - **ABVD x 2**
    - **PET-2 negative (Deauville 1-3)** → **BV + nivolumab x 3**
    - **PET-2 positive (Deauville 4,5)** → **BV+ AVD x 4 then nivolumab maintenance q 2 wks x 3 mo**
PET-based response after 2 cycles of brentuximab vedotin in combination with AVD for first-line treatment of unfavorable early-stage HL: A randomized phase II trial of LYSA-FIL-EORTC Intergroup

**BREACH Study schema**

**Standard arm**
- PET-CT 0
- PET-CT 2
- PET-CT 4*
- Radiotherapy 30Gy
- Refractory patients: Premature Withdrawal

**Arm A**
- Randomization
- ABVD
- C1
- C2
- C3
- C4
- Radiotherapy 30Gy
- PET-CT EoT

**Arm B**
- Randomization
- AVD + Brentuximab vedotin
- C1
- C2
- C3
- C4
- Radiotherapy 30Gy
- PET-CT EoT

**Experimental arm**
- BV 1.2 mg/kg every 2 weeks
- G-CSF mandatory

*: PET-CT 4 mandatory only for patient with PET-CT 2*
PET-based response after 2 cycles (IRC assessment)

| PET-response after 2 cycles, n(%) | BV-AVD  
| n=113 | ABVD  
| n=57 |
|---|---|---|
| Negative | 93 (82.3 %) | 43 (75.4 %) |

95% confidence interval | (75.3 % ; 88.0 %) | (64.3 % ; 84.5 %)

Negative PET defined as Deauville 1-3

The primary objective was met with a lower boundary of the 95% CI greater than 75% in the experimental arm.
Advanced HL (III-IV)

- **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, mechlorethamine, 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.
Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin’s Lymphoma

Peter Johnson, M.D., Massimo Federico, M.D., Amy Kirkwood, M.Sc., Alexander Fosså, M.D., Leanne Berkahn, M.D., Angelo Carella, M.D., Francesco d’Amore, M.D., Gunilla Enblad, M.D., Antonella Franceschetto, M.D., Michael Fulham, M.D., Stefano Luminari, M.D., Michael O’Doherty, M.D., Pip Patrick, Ph.D., Thomas Roberts, B.Sc., Gamal Sidra, M.D., Lindsey Stevens, Paul Smith, M.Sc., Judith Trotman, M.D., Zaid Viney, M.D., John Radford, M.D., and Sally Barrington, M.D.

Study Overview

- A randomized trial suggests that patients with negative PET-CT findings after two cycles of ABVD may have the bleomycin dropped from the regimen for the final four cycles.
- The omission of bleomycin reduced pulmonary toxic effects without reducing overall survival.
UK Advanced Stage HL Study
RATHL Study

937 patients (Europe/Australia/NZ)
IIB to IV pts, or IIA with bulky disease/3 sites
42% stage II
30% stage III
28% stage IV

Outcome

ABVD 85.7% vs AVD (84.4%)

ABVD (97.2%) vs AVD (97.6%)
Progression-free and Overall Survival.

A. Progression-free Survival among Patients with Negative PET Findings

B. Overall Survival among Patients with Negative PET Findings

C. Progression-free Survival among Patients with Positive PET Findings

D. Overall Survival among Patients with Positive PET Findings

## Adverse Events


<table>
<thead>
<tr>
<th>Event</th>
<th>ABVD, Cycles 1 and 2 (N=1203)</th>
<th>ABVD, Cycles 3–6 (N=468)</th>
<th>AVD, Cycles 3–6 (N=457)</th>
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</thead>
<tbody>
<tr>
<td>Any blood or bone marrow event</td>
<td>711 (59)</td>
<td>280 (60)</td>
<td>273 (60)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>694 (58)</td>
<td>275 (59)</td>
<td>269 (59)</td>
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<tr>
<td>Thrombocytopenia†</td>
<td>16 (1)</td>
<td>6 (1)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Any cardiac event</td>
<td>9 (1)</td>
<td>6 (1)</td>
<td>2 (&lt;0.5)</td>
</tr>
<tr>
<td>Any constitutional symptom</td>
<td>36 (3)</td>
<td>18 (4)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Fatigue†</td>
<td>14 (1)</td>
<td>14 (3)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Fever</td>
<td>16 (1)</td>
<td>4 (1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Any infection</td>
<td>76 (6)</td>
<td>68 (15)</td>
<td>47 (10)</td>
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<tr>
<td>Febrile neutropenia†</td>
<td>24 (2)</td>
<td>22 (5)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Any neurologic event</td>
<td>20 (2)</td>
<td>23 (5)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Any pulmonary or upper respiratory event†</td>
<td>8 (1)</td>
<td>15 (3)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Dyspnea†</td>
<td>5 (&lt;0.5)</td>
<td>9 (2)</td>
<td>1 (&lt;0.5)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>5 (1)</td>
<td>1 (&lt;0.5)</td>
</tr>
<tr>
<td>Any vascular event</td>
<td>18 (1)</td>
<td>23 (5)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Thrombosis or embolism related to vascular access</td>
<td>4 (&lt;0.5)</td>
<td>4 (1)</td>
<td>1 (&lt;0.5)</td>
</tr>
<tr>
<td>Thrombosis, thrombus, or embolism</td>
<td>14 (1)</td>
<td>20 (4)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Any clinical adverse event‡‡‡</td>
<td>188 (16)</td>
<td>143 (31)</td>
<td>96 (21)</td>
</tr>
<tr>
<td>Any grade 3 or 4 adverse event</td>
<td>771 (64)</td>
<td>322 (69)</td>
<td>299 (65)</td>
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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
CONSORT diagram demonstrating patient flow of 358 patients enrolled in the SWOG 0816 trial.
Overall and PFS of Advanced HL SWOG S0816

![Graph showing overall survival and progression-free survival over time after registration.]

- **Overall Survival**: 336 patients at risk, 17 failed, 2-year estimate = 98%
- **Progression-Free Survival**: 336 patients at risk, 79 failed, 2-year estimate = 79%

Published in: Oliver W. Press; Hongli Li; Heiko Schöder; David J. Straus; Craig H. Moskowitz; Michael LeBlanc; Lisa M. Rimsza; Nancy L. Bartlett; Andrew M. Evens; Erik S. Mittra; Ann S. LaCasce; John W. Sweetenham; Paul M. Barr; Michelle A. Fanale; Michael V. Knopp; Ariela Noy; Eric D. Hsi; James R. Cook; Mary Jo Lechowicz; Randy D. Gascoyne; John P. Leonard; Brad S. Kahl; Bruce D. Cheson; Richard I. Fisher; Jonathan W. Friedberg; *JCO 2016*, 34, 2020-2027.

DOI: 10.1200/JCO.2015.63.1119

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S0816 PFS by PET2 Result

Arm 1: Continued ABVD
Arm 2: eBEACOPP

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

Months After Registration
Progression-free survival of 331 patients with HL treated with response-adapted therapy on SWOG S0816 trial. Based on Deauville score at PET-2.
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. Can new agent add to ABVD improve Response rate? Echelon 1 trial (AVD + brentuximab vedotin vs. ABVD)

4. Can other salvage therapy be used for PET positive (ABVD + brentuximab vedotin for PET + patients)
FFS and OS for patients with advanced-stage classical HL after primary treatment with ABVD + brentuximab vedotin (ABVD+BV) or AVD + brentuximab vedotin (AVD+Bv).

- 51 patients
- Stage II bulky-IV
- ABVD+BV=25
- AVD+BV=26
- BV dose 0.6-1.2 mg/kg in ABVD; 1.2 mg/kg in AVD
- 2 deaths from pulmonary toxicity in ABVD

Joseph M. Connors et al. Blood 2017;130:1375-1377
Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin’s Lymphoma

The Phase 3 ECHELON-1 Study

Joseph M. Connors, M.D., Wojciech Jurczak, M.D., Ph.D., David J. Straus, M.D., Stephen M. Ansell, M.D., Ph.D., Won S. Kim, M.D., Ph.D., Andrea Gallamini, M.D., Anas Younes, M.D., Sergey Alekseev, M.D., Árpánd Illés, M.D., D.Sci., Marco Picardi, M.D., Ewa Lech-Maranda, M.D., Ph.D., Yasuhiro Oki, M.D., Tatyana Feldman, M.D., Piotr Smolewski, M.D., Ph.D., Kerry J. Savage, M.D., Nancy L. Bartlett, M.D., Jan Walewski, M.D., Robert Chen, M.D., Radhakrishnan Ramchandren, M.D., Pier L. Zinzani, M.D., Ph.D., David Cunningham, M.B. Ch.B., M.D., Andras Rosta, Ph.D., Neil C. Josephson, M.D., Eric Song, Ph.D., Jessica Sachs, M.D., Rachael Liu, Ph.D., Hina A. Jolin, Pharm.D., Dirk Huebner, M.D., John Radford, M.D., for the ECHELON-1 Study Group
ECHELON-1: Open-label, global, randomized, phase 3 study of A+AVD versus ABVD in patients with newly diagnosed advanced cHL

**Inclusion criteria**
- cHL stage III or IV
- ECOG PS 0, 1 or 2
- Age ≥18 years
- Measurable disease
- Adequate liver and renal function

218 study sites in 21 countries worldwide

**Screening CT/PET scan**

1:1 randomization (N=1334)

- ABVD x 6 cycles (n=670)
- A+AVD x 6 cycles (n=664)
  - Brentuximab vedotin: 1.2 mg/kg IV infusion Days 1 & 15

**EOT CT/PET scan**

Follow-up
- Every 3 months for 36 months, then every 6 months until study closure

**End-of-Cycle-2 PET scan**
- Deauville 5; could receive alternate therapy per physician’s choice (not a modified PFS event)
A modified PFS event was defined as the first of:
Progression/Death from any cause

- PET6 = D3, 4, 5 after completion of frontline therapy followed by subsequent anticancer therapy

**Per IRF**

| Dx | Tx | PET6 = D1, 2 | Follow-up | No modified PFS event |
| Dx | Tx | PET6 = D1, 2 | Tx | Follow-up | No modified PFS event |
| Dx | Tx | PET6 = D3, 4, 5 | Follow-up | No modified PFS event |
| Dx | Tx | PET6 = D1–5 | Follow-up | Modified PFS event |
| Dx | Tx | PET6 = D3, 4, 5 | Follow-up | Modified PFS event |
Modified Progression-free Survival in the Intention-to-Treat Population

**Modified PFS per independent review**

Time from randomization (months) vs. Probability of modified PFS.

- **HR 0.77 (95% CI: 0.60–0.98)**
- **Log-rank test p-value: 0.0348**

### Number of events

<table>
<thead>
<tr>
<th>Category</th>
<th>A+AVD</th>
<th>ABVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>90</td>
<td>102</td>
</tr>
<tr>
<td>Death</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Modified progression</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

### Modified PFS estimates

<table>
<thead>
<tr>
<th>Time</th>
<th>A+AVD (95% CI)</th>
<th>ABVD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year</td>
<td>82.1 (78.7–85.0)</td>
<td>77.2 (73.7–80.4)</td>
</tr>
</tbody>
</table>

Median follow-up (range): 24.9 months (0.0–49.3)
Most clinically important treatment-emergent adverse events
Incidence (any grade) ≥20% + febrile neutropenia

<table>
<thead>
<tr>
<th>Common adverse events, %*</th>
<th>A+AVD (N=662)</th>
<th>ABVD (N=659)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Any grade</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>54</td>
</tr>
<tr>
<td>Constipation</td>
<td>Any grade</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Any grade</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Any grade</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>Any grade</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Any grade</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>Any grade</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Any grade</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Any grade</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Any grade</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>2</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Any grade</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>19</td>
</tr>
</tbody>
</table>
Conclusion of ECHELON-1 Study

- A+AVD had superior efficacy 2-yrs PFS 82% vs. 77% with ABVD
- Neutropenia occurred in 58% of A+AVD vs. 45% ABVD, reduced with growth factor support
- Peripheral neuropathy occurred in 67% A+AVD vs. 43% ABVD
- The major cause of death in A+AVD was associated with neutropenia whereas the deaths in ABVD were associated with pulmonary toxicity
- The benefit of A+AVD was observed in patients with stage IV, > 1 extranodal sites and high risk IPI (4 to 7)
Survival: Older vs Younger HL

<table>
<thead>
<tr>
<th></th>
<th>&lt; 60 years</th>
<th>=/\ 60 years</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFS 3-year</td>
<td>76%</td>
<td>56%</td>
<td>0.002</td>
</tr>
<tr>
<td>FFS 5-year</td>
<td>74%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>OS 3-year</td>
<td>93%</td>
<td>70%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS 5-year</td>
<td>90%</td>
<td>58%</td>
<td></td>
</tr>
</tbody>
</table>

Evens AM et al. BJH 2013
Frontline Brentuximab Vedotin in combination with DTIC or Bendamustine in patients ≥60 years with Hodgkin Lymphoma

Jonathan W. Friedberg et al. Blood 2017;130:2829-2837

BV, brentuximab vedotin, CT, computed tomography; DTIC, dacarbazine; PET, positron emission tomography; RT, radiotherapy

a BV (≥16 cycles) in combination with DTIC (12 cycles) or bendamustine (6 cycles)
b Consolidative RT allowed after combination (≥3 weeks after BV+DTIC), then BV allowed after RT (≥2 weeks after RT for BV+bendamustine arm)
c During treatment, CT at Cycles 4 and 12; CT and PET at Cycles 2, 8, and at end of treatment (no PET after CR); CT at Cycle 16 if eligible for continued treatment, then per institutional standard of care or at least every 6 cycles. During follow-up, CT at least every 6 months for first 2 years, then at third year, then per institutional standard of care until progression; lymphoma assessments at least approximately every 6 months
PFS of treatment-naive, elderly patients with HL treated with BV plus bendamustine.

Jonathan W. Friedberg et al. Blood 2017;130:2829-2837
PFS of treatment-naive, elderly patients with HL treated with BV plus DTIC. PFS was analyzed using Kaplan-Meier methodology.

Jonathan W. Friedberg et al. Blood 2017;130:2829-2837
PFS of CR vs non-CR in elderly patients with HL treated with BV plus DTIC. Censored patients are indicated on the graph.

Jonathan W. Friedberg et al. Blood 2017;130:2829-2837

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Sequential Brentuximab Vedotin (Adcetris®)
Before and After Adriamycin, Vinblastine,
and Dacarbazine (Bv-AVD) for Older Pts with
Untreated Hodgkin Lymphoma (HL): Final
Results from a Multicenter Phase II Study

Andrew M. Evens¹, Ranjana H. Advani², Michelle
Fanale³, Sonali M. Smith⁴, Borko Jovanovic, PhD⁵, Irene
Helenowski, PhD⁵, Gregory Bociek⁶, Andreas K. Klein¹,
Jane N. Winter⁷, Leo I. Gordon⁷, and Paul A. Hamlin⁸

(1) Tufts Medical Center, Boston, MA; (2) Stanford University, Stanford, CA; (3) MD Anderson
Cancer Center, Houston, TX; (4) University of Chicago, Chicago, IL; (7) Preventive Medicine,
Northwestern University, Chicago, IL; (6) University of Nebraska, Omaha, NE; (7) Northwestern
University, Chicago, IL; (8) Memorial Sloan Kettering Cancer Center, New York, NY

ASH 2017, Atlanta, Abstract #89
Incorporation of Brentuximab Vedotin into Frontline Therapy

**METHODS**
- Simon 2-stage with plan of 48 total pts
- Primary endpoint: complete remission (CR) rate after AVD
  - If ≥12 CRs among 20 evaluable pts, accrual continued to 2\textsuperscript{nd} stage (evaluable = 2 cycles of AVD therapy)
- Lugano criteria utilizing FDG-PET/CT (with Deauville criteria)

**PET1 and CT1 (Staging)**

- **BV x 2 cycles**
  - (1.8 mg/kg q 3 wks)

**PET2 (first 22pts)**

- **AVD x 6 cycles**

**CT + PET (all pts)**

- **BV consolidation**
  - (1.8 mg/kg q 3 wks x4)

Evens et al. ASH 2017, Abstract 733
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=48 (median)</th>
<th>Percent (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median 69 years</td>
<td>60-88 yrs</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 63%</td>
<td>Female 37%</td>
</tr>
<tr>
<td>Histology</td>
<td>NS 46%</td>
<td>MC 25%</td>
</tr>
<tr>
<td></td>
<td>cHD 25%</td>
<td>LR 4%</td>
</tr>
<tr>
<td>EBV EBER</td>
<td>14</td>
<td>30%</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>Median 1</td>
<td>21% PS=2</td>
</tr>
<tr>
<td>Bone marrow (+)</td>
<td>11</td>
<td>23%</td>
</tr>
<tr>
<td>Stage III / IV</td>
<td>39</td>
<td>82%</td>
</tr>
<tr>
<td>IPS</td>
<td>Median 4</td>
<td>3-7 in 58%</td>
</tr>
<tr>
<td>Functional status</td>
<td>Median CIRS 6</td>
<td>52% Grade 3-4</td>
</tr>
<tr>
<td></td>
<td>Geriatric syndrome</td>
<td>8% Grade 3-4</td>
</tr>
<tr>
<td></td>
<td>Loss of IADLs</td>
<td>12%</td>
</tr>
</tbody>
</table>

Evens et al. ASH 2017, Abstract 733
Results: Efficacy

(N=48) BV x 2 ➔ AVD x 3 ➔ AVD x 3 ➔ BV x 4

ORR 87% CR 30%
(PET)

ORR 98% CR 76%

ORR 95% CR 90%

ORR 95% CR 93%

ITT (n=48) after 6 AVD: ORR 88% and CR 81%
Adverse Events

- 52% completed therapy
- 42% of pts had SAE
- Grade 2 PN in 33% pts (27% sensory)
  - Majority reversible

<table>
<thead>
<tr>
<th>Grade 3/4 SAE</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>15%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>6%</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>6%</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>6%</td>
</tr>
<tr>
<td>UTI</td>
<td>6%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6%</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>4%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>4%</td>
</tr>
<tr>
<td>Pruritis</td>
<td>2%</td>
</tr>
</tbody>
</table>
Survival: PFS and OS

2-Year PFS 85% and 2-year OS 94% (ITT)
Median F/U 28 months

Evens et al. ASH 2017, Abstract 733
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>Salvoage 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>

Aug ICE 60%
IGEV 53.8%

Moskowitz CH et al. Blood. 2001
Santoro A et al. Haematologica 2007
Kuruvilla J et al. Cancer
Moskowitz A et al. Blood 2010
How improve the outcome of Auto-SCT for Hodgkin lymphoma

**Improve salvage regimens to achieve remission before transplant**
- Clinical trials new agents

**Improve Conditioning regimens**
- Tandem transplant
- New preparative regimens

**Consolidation Therapy post transplant to prevent relapse**
- Brentuximab vedotin post-transplant
- Checkpoint inhibitor targeting PD-1 or PDL-1
PET-Adapted Second-Line Therapy for Relapsed/Refractory HL

MSKCC 04-047

ICE-based SLT

+ → PET → -

GVD

HDT/ASCR

Event Free Survival by Pre-ASCT Response

(1) FDG-PET neg after GVD: 17 pts; 14 censored

(2) FDG-PET neg after ICE: 59 pts; 46 censored

(3) FDG-PET pos after GVD or ineligible: 21 pts; 6 censored

Log Rank Test

(1) vs (2): p=0.715
(1) vs (3): p=0.001
(2) vs (3): p<0.001
(1) vs (2) vs (3): p<0.001

Time (years)

Cumulative Survival (%)

Further therapy in PET+ patients improved outcome in 44% (17/38)

Brentuximab Vedotin Mechanism of Action

Brentuximab vedotin (SGN-35) ADC monomethyl auristatin E (MMAE), potent antitubulin agent protease-cleavable linker anti-CD30 monoclonal antibody

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

- Antibody drug conjugate that selectively delivers the antimicrotubule agent, monomethyl auristatin E, into CD30-expressing cells
- Phase 2 trial of patients with relapsed/refractory HL after auto-SCT (n=102) treated with BV
  - ORR: 75%
  - CR: 34%
  - mDOR: 20.5 mo
  - Gr 3/4 AEs: 55%

5-Year PFS of patients treated with Brentuximab vedotin after failure of auto-SCT
• BV given at 1.8 mg/kg IV outpatient every 3 weeks for 4 cycles max
• No premedication with first cycle
City of Hope: Auto-SCT after BV as first-line Salvage Therapy

Cumulative Incidence / Survival Probability

Time (Months) from Transplant

Overall Survival
Progression Free Survival
Non-Relapse Mortality

Median f/u | 27.3 Months
--- | ---
OS | 93.6%
PFS | 71.9%
NRM | D100 -3.1%

Herrera et al, Cologne 2016
Brentuximab Vedotin as Second-Line Therapy in Relapsed/Refractory HL

Weekly BV x 2 cycles

+ PET

Augmented ICE x 2 cycles

- PET

Further treatment according to treating physician

HDT/ASCT
Phase 2 study of BV followed by Augmented ICE in Relapsed Refractory HL

46 patients
12 (27%) PET neg after BV
32 (73%) PET pos received Augmented ICE
34 were PET neg
44 underwent Auto-SCT
Brentuximab Vedotin Plus Chemotherapy

- **First Line Treatment**
  - BV +AVD
  - BV+BEACOPP

- **Salvage Therapy**
  - BV plus Bendamustine (LaCasce, et al. ; O’Connor et al.)
    - Phase II, 55 patients, 51% relapsed, 49% IF
    - BV 1.8 mg/kg day1, Benda 90 mg/m2 day 1-2
    - ORR 93%, CR 74%, 12 month PFS 80%
  - BV+ICE (Cassaday, R. et al)
    - BV day 1, 8 + ICE day 1-3
    - 16 patients (65% IF); Overall response =94%, 88% CR, 12 proceeded to auto-SCT
  - BV plus ESHAP (Garcia-Sanz et al.)
    - 66 patients
    - ORR 96%, CR 70%
    - 61 proceeded to auto-SCT, PFS at 1 year was 87%
The Microenvironment in HL

- Reed-Sternberg cells comprise 0.1%-2% of total tumor bulk
- The remainder are cells of the patients' immune system that facilitate the HRS cells in evading immune detection

Reproduced with permission of American Society for Clin Invest, from Hodgkin lymphoma, Küppers R, et al., 122, 2012; permission conveyed through Copyright Clearance Center, Inc.

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

Introduction

- Immune checkpoint blockade is now a treatment option in relapsed/refractory classical Hodgkin lymphoma
  - Pembrolizumab is approved by the FDA for the treatment of adult and pediatric patients with refractory classical HL, or those who have relapsed after 3 or more prior lines of therapy
  - Nivolumab is approved by the FDA for patients with classical HL that has relapsed or progressed after autologous HSCT and post-transplantation brentuximab vedotin

- Other immunotherapy approaches are also under investigation, as is the use of immunotherapy earlier in the course of the disease
Phase 2 Trials: Pembrolizumab

- KEYNOTE-087: phase 2 trial of pembrolizumab in patients with relapsed/refractory HL (N=210)
  - ORR: 69.0%; CR: 22.4%
  - mOS: NR
  - Gr 3/4 TRAEs: 6.4%

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (after ASCT and subsequent BV) (n=69)</th>
<th>Cohort 2 (ineligible for ASCT; after salvage chemo and BV) (n=81)</th>
<th>Cohort C (after ASCT, no BV) (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>73.9</td>
<td>64.2</td>
<td>70.0</td>
</tr>
<tr>
<td>CR, %</td>
<td>21.7</td>
<td>24.7</td>
<td>20.0</td>
</tr>
<tr>
<td>mDOR, mo</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Phase 2 Trials: Nivolumab**

- **CheckMate 205**: Phase 2 trial of nivolumab in patients with recurrent classical HL who relapsed after ASCT (n=243)

<table>
<thead>
<tr>
<th></th>
<th>Cohort A (BV-naïve) (n=63)</th>
<th>Cohort B (ASCT followed by BV) (n=80)</th>
<th>Cohort C (BV before and/or after ASCT) (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>65</td>
<td>68</td>
<td>73</td>
</tr>
<tr>
<td>CR, %</td>
<td>29</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>mDOR, mo</td>
<td>20</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>mPFS, mo</td>
<td>18.3</td>
<td>14.7</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Interim Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

Alex F. Herrera¹, Alison J. Moskowitz², Nancy L. Bartlett ³, Julie M. Vose⁴, Radhakrishnan Ramchandren⁵, Tatyana A. Feldman⁶, Ann S. LaCasce⁷, Stephen M. Ansell⁸, Craig H. Moskowitz², Keenan Fenton⁹, Carol Anne Ogden⁹, David Taft⁹, Qu Zhang⁹, Kazunobu Kato¹⁰, Mary Campbell⁹, Ranjana H. Advani¹¹

¹City of Hope National Medical Center, Duarte, CA, USA; ²Memorial Sloan Kettering Cancer Center, New York, NY, USA; ³Washington University School of Medicine, St. Louis, MO, USA; ⁴University of Nebraska Medical Center, Omaha, NE, USA; ⁵Karmanos Cancer Institute, Detroit, MI, USA; ⁶Hackensack University Medical Center, Hackensack, NJ, USA; ⁷Dana Farber Cancer Institute, Boston, MA, USA; ⁸Mayo Clinic, Rochester, MN, USA; ⁹Seattle Genetics, Inc., Bothell, WA, USA; ¹⁰Bristol-Myers Squibb, Princeton, NJ, USA; ¹¹Stanford University Medical Center, Palo Alto, CA, USA

American Society of Hematology Annual Meeting; Atlanta, Georgia, December 9–12, 2017, Abstract #649
Methods

Patients received treatment every 3 weeks (1 cycle) for up to 12 weeks (4 cycles)

- Cycle 1: BV was given on Day 1 and Nivo on Day 8
- Cycles 2–4: Both BV and Nivo were given on Day 1

After completion of the EOT response assessment, patients were eligible to undergo autologous stem cell transplant (ASCT)

AEs were recorded from the start of treatment through 100 days post last dose of Nivo including the ASCT period, as applicable
Phase 1/2 study of BV + Nivolumab

Results

- 62 patients, 58 completed treatment
- 45% primary refractory, 31% relapsed < 1 year
- Objective response 85%, CR 62%, 22% PR
- 39 went on to auto-SCT
- No impact on stem cell collection or engraftment
- Immune-related AE occurred in 84%
- Infusion-related reaction occurred in 41%
Moving Checkpoint Inhibition Earlier in the Disease

- Research is ongoing into whether checkpoint inhibition has a role earlier in the course of the disease

- Nivolumab + AVD\(^a\)
  - CheckMate 205, phase 2, cohort of patients with newly diagnosed HL to receive nivolumab + AVD

- Brentuximab + nivolumab\(^b\)
  - phase 2 trial of BV + nivolumab in patients with untreated HL unable to receive standard ABVD

---

\(^a\) ClinicalTrials.gov. NCT02181738. \(^b\) ClinicalTrials.gov. NCT02758717.
The AETHERA Trial: Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Brentuximab Vedotin vs. Observation post autologous SCT in Patients with high-risk relapsed/refractory HL

- Conducted at 78 sites in North America and Europe
- Patients were required to be primary-refractory, have relapsed <12 months from frontline therapy, or have had extranodal involvement
- Patients must also have had at least a response of stable disease (SD) following pre-ASCT salvage chemotherapy
Progression-Free Survival

**PFS per IRF**

![Graph showing PFS per IRF](image)

<table>
<thead>
<tr>
<th>Brentuximab vedotin (N=165)</th>
<th>Placebo (N=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.57 (0.40–0.81, P=0.001)</td>
</tr>
<tr>
<td>Events</td>
<td>60</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>43</td>
</tr>
<tr>
<td>2-year PFS rate</td>
<td>63%</td>
</tr>
</tbody>
</table>

**PFS per Investigator†**

![Graph showing PFS per Investigator†](image)

<table>
<thead>
<tr>
<th>Brentuximab vedotin (N=165)</th>
<th>Placebo (N=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.50 (0.36–0.70)</td>
</tr>
<tr>
<td>Events</td>
<td>60</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>--</td>
</tr>
<tr>
<td>2-year PFS rate</td>
<td>65%</td>
</tr>
</tbody>
</table>

* Regularly scheduled CT scans
† Includes information from both radiographic assessments and clinical lymphoma assessments
PFS by Eligible Criteria

Moskowitz et al.

N=196

N=107

N=26

Percent of Patients Free of PD or Death

Time (Months)

Brentuximab vedotin

Placebo

Refractory

Relapse <12 Months

Relapse ≥12 Months (with extranodal disease)
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 for Relapsed HL

<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%</td>
<td>MUD: 2 yr, 8%</td>
<td>MRD: 2 yr, 23%</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
<table>
<thead>
<tr>
<th>Group</th>
<th>Conditioning</th>
<th>GVHD</th>
<th>NRM</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>Flu/Cy/TBI</td>
<td>CsA or Tac MMF PT-Cy</td>
<td>2 yr, 26%</td>
<td>2 yr, 66%</td>
<td>2 yr, 54%</td>
</tr>
<tr>
<td>Italian</td>
<td>Flu/Cy/TBI + Thiotepa</td>
<td>CsA or Tac MMF PT-Cy</td>
<td>2 yr, 4%</td>
<td>4 yr, 77%</td>
<td>4 yr, 63%</td>
</tr>
<tr>
<td>French</td>
<td>Flu/Cy/TBI</td>
<td>CsA or Tac MMF PT-Cy</td>
<td>3 yr, 9%</td>
<td>3 yr, 75%</td>
<td>3 yr, 66%</td>
</tr>
<tr>
<td>Spanish</td>
<td>Flu/Cy/Bu</td>
<td>CsA or Tac MMF PT-Cy</td>
<td>1 yr, 21%</td>
<td>2 yr, 48%</td>
<td>2 yr, 58%</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%
Immunotherapy and Allo-HCT

- Allogeneic HCT includes the risk for GVHD
- Questions remain about the safety of using PD-1 inhibition with allo-HCT
- Retrospective trial looked at 31 patients (29 with classical HL) receiving PD-1 blockade after allo-HCT
  - ORR: 77%
  - At last follow-up (median 428 days):
    - 11 of 31 patients had disease progression
    - 21 of 31 patients (68%) were still alive
    - 17 patients (55%) developed treatment-emergent GVHD after PD-1 inhibition
    - 8 patients (26%) died due to new-onset GVHD disease after PD-1 inhibition

CAR T Cells Targeting CD30

- Phase 1 dose escalation study of 9 patients with relapsed/refractory HL (n=7) or ALCL were infused with autologous T cells gene-modified with retroviral vector to express the CD30-specific CAR
- All other therapy was discontinued at least 4 weeks before
  - CR in 2 of 7 patients
  - No toxicities were attributable to CD30 CAR T cells
- Further research is necessary to see whether CAR T cell therapy has a role in HL

Treatment Guidelines

- **Limited Stage Favorable**
  - ABVD x 2 + 20 cGY XRT
  - ABVD x 2 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

  Clinical Trials 
  Or BV+AVD
Treatment Guidelines for Relapsed or Refractory Hodgkin Lymphoma

**Relapsed Refractory to induction**

1) Brentuximab vedotin
2) Pembrolizumab or nivolumab
3) Clinical trial
4) Salvage chemotherapy
5) Local radiation

**Not Auto-SCT candidate**

1) Brentuximab vedotin
2) Pembrolizumab or nivolumab
3) ICE or gemcitabine based chemotherapy

**if SD/PD then**
1) Brentuximab vedotin, if no prior exposure or prior response
2) Pembrolizumab or nivolumab
3) Clinical trial
4) Salvage chemotherapy
5) Allo-HCT

**CR/PR Auto-SCT**