Advanced stage HL
The old and new match: BEACOPP

Peter Borchmann
German Hodgkin Study Group
University of Cologne, Germany
1. In a treatment related mortality rate of 0.8%.
2. In an overall survival at 5 years of 95%.
3. In an infertility rate of about 80% in women in the age of 25 years at diagnosis.
4. In 0.3% secondary acute myeloid leukemia.

Which answer is wrong? For patients with advanced stage HL, treatment with 6 cycles BEACOPPesc, the GHSG standard of care, results
1. Positive early interim PET (after cycle 2) identifies a high risk group of patients

2. Residual disease is defined as any tumor > 1.5 cm at the end of chemotherapy

3. PET after the end of chemotherapy helps to identify a high risk group

4. As compared to treatment with ABVD, the superiority of BEACOPP in terms of PFS and OS is both significant and relevant in IPI low risk patients.
The old and new match: BEACOPP

1. Why do I like BEACOPPesc?
2. Why do I prefer BEACOPPesc over ABVD?
3. Can we do even better than BEACOPPesc?
I like BEACOPPesc, because it is very active.

The GHSG HD9 trial

I like BEACOPP, because my patients ask for cure.

The GHSG HD9 trial

I like BEACOPP, because it has been nicely developed: step by step, for 20 years now, including more than 5,000 patients.

The HD15 Study Design

8x BEACOPP escalated

6x BEACOPP escalated

8x BEACOPP Baseline-14

Restaging: PR and residual tumor >2.5 cm?

No

Follow up

Yes

PET

PET -

PET +

Rx 30Gy residual tumor

Engert et al., Lancet, 2012
I like BEACOPPesc, because only 11% of my patients will need Rx. Based on evidence, not on NCCN guidelines only ;- )

Negative Predictive Value of PET @12m: 94% (95% CI: 92 to 96%)
I just like it, because only 6 quick courses are even better than 8

![Graph showing the comparison of treatment outcomes]

- **PFS at 5 years:** 91%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>P-value</th>
<th>60 months difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vs. B</td>
<td>0.009</td>
<td>4.9% 97.5%-CI: [0.5%, 9.3%]</td>
</tr>
<tr>
<td>A vs. C</td>
<td>0.5</td>
<td>1.1% 97.5% CI: [-3.7%, 5.8%]</td>
</tr>
<tr>
<td>C vs. B</td>
<td>0.04 (n.s.)</td>
<td>3.9% 97.5% CI: [-0.5%, 8.6%]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time [months]</th>
<th>Pts. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8 Besc  711</td>
</tr>
<tr>
<td>12</td>
<td>6  Besc  644</td>
</tr>
<tr>
<td>24</td>
<td>7 B 14   630</td>
</tr>
<tr>
<td>36</td>
<td>5 B 14   567</td>
</tr>
<tr>
<td>48</td>
<td>4 B 14   455</td>
</tr>
<tr>
<td>60</td>
<td>3 B 14   301</td>
</tr>
<tr>
<td>72</td>
<td>2 B 14   158</td>
</tr>
<tr>
<td>84</td>
<td>1 B 14   84</td>
</tr>
</tbody>
</table>
and because I don’t like funerals
1. Why do I like BEACOPPesc?

2. Why do I prefer BEACOPPesc over ABVD?

3. Can we do even better?

Because my patients ask for cure first and foremost and I can offer cure using BEACOPP with the by far highest likelihood. That’s why.
The old and new match: BEACOPP

1. Why do I like BEACOPPesc?

2. Why do I prefer BEACOPPesc over ABVD?

3. Can we do even better?
Because it is just better: as shown by 4 out of 4 (yes, all!) controlled and randomized studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>n</th>
<th>5-y PFS</th>
<th>Difference (%)</th>
<th>p</th>
<th>5-y OS</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD 2000</td>
<td>ABVD</td>
<td>99</td>
<td>68</td>
<td></td>
<td></td>
<td>84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BEACOPP (4 esc + 2 std)</td>
<td>98</td>
<td>81</td>
<td>13</td>
<td>0.038</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>IIL †</td>
<td>ABVD</td>
<td>168</td>
<td>73</td>
<td></td>
<td></td>
<td>84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BEACOPP (4 esc + 4 std)</td>
<td>163</td>
<td>85</td>
<td>12</td>
<td>0.004</td>
<td>89</td>
<td>5</td>
</tr>
<tr>
<td>IG 20012 ‡ IPS 3-7</td>
<td>ABVD</td>
<td>275</td>
<td>69</td>
<td></td>
<td></td>
<td>86,7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BEACOPP (4 esc + 4 std)</td>
<td>274</td>
<td>84</td>
<td>15</td>
<td>0.0003</td>
<td>90,3</td>
<td>4</td>
</tr>
<tr>
<td>LYSA H34 IPS 0-2</td>
<td>ABVD</td>
<td>77</td>
<td>75</td>
<td></td>
<td></td>
<td>92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BEACOPP (4 esc + 4 std)</td>
<td>68</td>
<td>93</td>
<td>18</td>
<td>0.008</td>
<td>99</td>
<td>7</td>
</tr>
<tr>
<td>HD15</td>
<td>6 BEACOPPesc</td>
<td>711</td>
<td>91</td>
<td></td>
<td></td>
<td>95.3</td>
<td></td>
</tr>
</tbody>
</table>

†7-year PFS; ‡ 4-year PFS.
You still don’t believe it? Let’s have a look at the highest level of evidence: a metanalysis.

- 1,984 references were identified, referring to
- 77 publications,
- reporting 14 trials,
- evaluating 11 different regimens with a total of
- 10,011 patients and
- 47,033 patient-years of follow-up evaluable for the analyses of survival outcomes
- including 1,189 events with a
- average median follow-up 5.9 years

Skoetz et al., Lancet Oncol, 2012
BEACOPPesc is not just better. It is *much* better than ABVD ;-

<table>
<thead>
<tr>
<th>Regimen</th>
<th>5-year OS difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6*BEACOPPesc</td>
<td>10% (95% CI: 13% to 5%)</td>
</tr>
</tbody>
</table>
And BEACOPPesc is very safe!

For the vast majority of patients TRM is not a relevant problem at all.

TRM according individual risk score: age (>40, > 50, WHO PS 2)
Another surprise: neither more secondary neoplasia nor more sAML/MDS than with ABVD!

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>n</th>
<th>TRM (%)</th>
<th>sAML/MDS (%)</th>
<th>Second neoplasia n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD 2000</td>
<td>ABVD</td>
<td>99</td>
<td>n.r.</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>BEACOPP (4 esc + 2 std)</td>
<td>98</td>
<td>n.r.</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>IIIL†</td>
<td>ABVD</td>
<td>168</td>
<td>1</td>
<td>1</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td></td>
<td>BEACOPP (4 esc + 4 std)</td>
<td>163</td>
<td>3</td>
<td>1</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>IG 20012 ‡</td>
<td>ABVD</td>
<td>275</td>
<td>3.3</td>
<td>0.7</td>
<td>8 (2.9)</td>
</tr>
<tr>
<td>IPS 3-7</td>
<td>BEACOPP (4 esc + 4 std)</td>
<td>274</td>
<td>2.2</td>
<td>1.5</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>LYSA H34</td>
<td>ABVD</td>
<td>77</td>
<td>0</td>
<td>0</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>IPS 0-2</td>
<td>BEACOPP (4 esc + 4 std)</td>
<td>68</td>
<td>0</td>
<td>0</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>HD15</td>
<td>6 BEACOPPesc</td>
<td>711</td>
<td>0.8</td>
<td>0.3</td>
<td>15 (2.1)</td>
</tr>
</tbody>
</table>

†7-year PFS; ‡ 4-year PFS.
But: „Almost all patients become infertile after BEACOPPesc!“ True or not? Looking at data can help, if one wants to know ;-) 

More facts? Patients themselves do not rank fertility issues over disease control (Turner et al., 1996). In addition, only 1/6 of our patients do have an unfulfilled wish for parenthood. For the vast majority of patients, survival is upmost important for different reasons, often because they have kids already. We can trust our patients and can make shared decisions!

Behringer et al., JCO, 2013
1. Why do I like BEACOPPesc?

2. Why do I prefer BEACOPPesc over ABVD?

3. Because this is very reasonable. Much better survival, no more relevant toxicities.
1. Why do I like BEACOPPesc?

2. Why do I prefer BEACOPPesc over ABVD?

3. Can we do even better?
Which tools do we have to improve our regimen?

ABVD (E2496)

- PFS (stage III/IV) @3 y: 71% (29% failure rate)
- Escalation (PFS)
- PET guided
- Brentuximab

6x BEACOPPesc (HD15)

- PFS (stage III/IV) @3 y: 91% (9% failure rate)
- De-escalation (tox)
- PET guided
- Brentuximab
HD18: testing a PET guided treatment strategy

End of therapy AND residual nodes > 2.5 cm: PET positive: Rx

2 x BEACOPP escalated

centrally reviewed PET

PET +

1x BEACOPPesc

5x R-BEACOPPesc

1x BEACOPPesc

5x BEACOPPesc

Borchmann et al., ASH, 2014, abs 500
Assumptions and primary objective

1. Total 5-year PFS with 8x BEACOPPesc. is 86.3% (HD9/12)

2. 30% of patients will be PET positive after 2 courses (SUV uptake above mediastinal bloodpool)

3. 70% of all events will occur in PET-2 positive patients, resulting in a five year PFS of 68% for these patients

> Show that the addition of rituximab to our standard chemotherapy BEACOPPesc (R-BEACOPP) improves 5-year PFS to 83% (hazard ratio 0.483, i.e. rituximab more than halves the hazard)
PFS of iPET positive patients in HD18

Borchmann et al., ASH, 2014, abs 500

Interim PET positivity does not define a high risk cohort!
GHSG HD 18 trial

randomization

2 x BEACOPP

centrally reviewed PET

negative

4 x BEACOPP

2 x BEACOPP

Enrollment recently finished with 2104 patients’. Results available not before 2017.

PET negative: Follow up
The CD30 antigen: targeting the H-RS cell in HL with antibodies
Remodeling BEACOPPesc with Brentuximab vedotin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day</th>
<th>6x BEACOPP</th>
<th>6x BrECADD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>8</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>1-3</td>
<td>200</td>
<td>150</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>1</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2</td>
<td>1250</td>
<td>1250</td>
</tr>
<tr>
<td>Vincristine</td>
<td>8</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td><strong>Brentuximab vedotin</strong></td>
<td>1</td>
<td></td>
<td>1.8</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>1-7</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>1-14</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td><strong>Dacarbazine</strong></td>
<td>2-3</td>
<td></td>
<td>250</td>
</tr>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>1-4</td>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>
1. an efficacy comparable to BEACOPPesc (BrECADD, n=37, CR n=35 (95%), PR n= 2 (5%))

2. a safety profile superior to BEACOPPesc (grade 3 or 4 non-hematological toxicity 3% with

3. only 30% grade 1 or 2 neurotoxicity

6x BEACOPPesc will be challenged by 6x BrECADD in the international GHSG HD21 study starting soon.
How can we do better? Co-primary objectives in HD21

**Primary objectives:** to show

- Non-inferiority of BrECADD in terms of **PFS (observed in HD15: 91% stage II/IV at 3 years)**
- Superiority of BrECADD regarding **treatment-related morbidity (TRM) at end of treatment**

What do you think: how does this endpoint compare to the primary endpoint of ECHELON I, which is: improving the PFS at 3 years from 75% for ABVD to 82,5% for AVD-A? Honestly: how relevant is this objective taking into account some more relevant toxicities as neuropathy (roughly 75%)?
The old and new match: BEACOPPPesc

1. Why do I like BEACOPPPesc?

2. Why do I prefer BEACOPPPesc over ABVD?

3. Can we do even better than BEACOPPPesc?

We should always try to improve our treatment strategies, of course. However, any new strategy must be better in terms of overall survival than BEACOPPPesc: Patients want to be cured!
We, the GHSG, thank you for your attention!
Which answer is correct? In advanced stage HL treated with BEACOPPEesc,

1. Positive early interim PET (after cycle 2) identifies a high risk group of patients

2. Residual disease is defined as any tumor > 1.5 cm at the end of chemotherapy

3. PET after the end of chemotherapy helps to identify a high risk group

4. As compared to treatment with ABVD, the superiority of BEACOPP in terms of PFS and OS is both significant and relevant in IPI low risk patients.
Which answer is wrong? For patients with advanced stage HL, treatment with 6 cycles BEACOPPesc, the GHSG standard of care, results in:

1. In a treatment related mortality rate of 0.8%.
2. In an overall survival at 5 years of 95%.
3. In an infertility rate of about 80% in women in the age of 25 years at diagnosis.
4. In 0.3% secondary acute myeloid leukemia.
Future developments?

**ABVD escalation (PFS)**
- PET guided
- Numerous IITs ongoing
- ECHELO N-1 (AVD-A vs ABVD, Takeda sponsored)
- X Plus A(B)VD versus ABVD

**BEACOPP de-escalation**
- PET guided
- BV
- PD1-Ab
- Lysa AHL 2011 (2BEA + 4ABVD)
- tBEACOPP
- ?
- HD18 (4BEA)
- HD21 (BEACOPP vs BrECADD)
Current international developments

ABVD escalation (PFS)
- PET guided
- Brentuximab
- Numerous IITs ongoing
- ECHELON-1 (AVD-A vs ABVD, Takeda sponsored)

BEACOPP de-escalation
- PET guided
- Brentuximab
- Lysa AHL 2011 (2BEA + 4ABVD)
- HD18 (4BEA)
- tBEACOPP
- HD21 (BEACOPP vs BrECADD)
5y-OS of 88% (84-91%) is the estimate for ABVD for this analysis (reference value)
Probability for superiority of a BEACOPP containing over ABVD regimen is 100%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard ratio (95% CI)</th>
<th>Prob. best</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD (comparator)</td>
<td>1.0</td>
<td>0%</td>
</tr>
<tr>
<td>MOPP</td>
<td>1.40 (0.84 to 2.32)</td>
<td>0%</td>
</tr>
<tr>
<td>MOPP/ABV</td>
<td>0.98 (0.70 to 1.41)</td>
<td>0%</td>
</tr>
<tr>
<td>C(M)OPP/ABVD</td>
<td>1.19 (0.82 to 1.66)</td>
<td>0%</td>
</tr>
<tr>
<td>8*BEACOPPbase</td>
<td>1.07 (0.65 to 1.78)</td>
<td>0%</td>
</tr>
<tr>
<td>8*BEACOPPesc</td>
<td>0.63 (0.42 to 0.98)</td>
<td>1%</td>
</tr>
<tr>
<td>Stanford V</td>
<td>0.96 (0.68 to 1.37)</td>
<td>0%</td>
</tr>
<tr>
<td>C(M)OPP/EBV/CAD</td>
<td>1.14 (0.66 to 1.98)</td>
<td>0%</td>
</tr>
<tr>
<td>4<em>BEACOPPesc + 2-4</em>BEACOPPbase</td>
<td>0.75 (0.52 to 1.10)</td>
<td>1%</td>
</tr>
<tr>
<td>8*BEACOPP-14</td>
<td>0.43 (0.22 to 0.86)</td>
<td>35%</td>
</tr>
<tr>
<td>6*BEACOPPesc</td>
<td>0.38 (0.20 to 0.75)</td>
<td>63%</td>
</tr>
</tbody>
</table>
## Treatment outcome after chemotherapy (primary endpoint)

<table>
<thead>
<tr>
<th>Treatment Outcome</th>
<th>BrECAPP N = 33</th>
<th>BrECADD N = 37</th>
<th>Total N = 70</th>
<th>HD18 (6 cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR or PET negative PR</td>
<td>28 (85%)</td>
<td>35 (95%)</td>
<td>63 (90%) (97.5%-CI 80%-96%)</td>
<td>91,9%</td>
</tr>
<tr>
<td>Less than PR or PET positive (above liver)</td>
<td>5 (15%)</td>
<td>2 (5%)</td>
<td>7 (10%) (97.5%-CI 4%-20%)</td>
<td>7 %</td>
</tr>
</tbody>
</table>

The lower limit of the one-sided 95% confidence interval for the number of treatment successes is 80.5%.
## Acute Toxicities
### 6x BRECADD (n=38)

<table>
<thead>
<tr>
<th>Type of Toxicity</th>
<th>NCIC-CTC Grade</th>
<th>HD18+ III/IV (n=447)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>none</td>
<td>I</td>
</tr>
<tr>
<td>Hematological</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Organs</td>
<td>16 (42%)</td>
<td>14 (37%)</td>
</tr>
</tbody>
</table>
Neurotoxicity with tBEACOPP (n=71, all patients after 6 cycles)

<table>
<thead>
<tr>
<th>Type of Toxicity</th>
<th>NCIC-CTC Grade</th>
<th>HD18* III/IV (n=447)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>none</td>
<td>I</td>
</tr>
<tr>
<td>Nervous system (sensory)</td>
<td>49 (69%)</td>
<td>14 (20%)</td>
</tr>
<tr>
<td>Nervous system (mot.)</td>
<td>70 (99%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

In the entire study cohort, 22/71 patients showed grade 1 or 2 neurotoxicity, i.e. 30% (73% with AVD-A)
randomization

2 x BEACOPP esc

centrally reviewed PET

4x BEACOPP esc

2 x BrECADD

4x BrECADD

End of therapy AND residual nodes > 2.5 cm:

PET positiv: Rx

PET negative: Follow up
Can we further improve the efficacy of BEACOPPesc?

Standard treatment defining study result:

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Median FU</th>
<th>n</th>
<th>PFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HD15</strong></td>
<td>6x BEACOPPesc</td>
<td>60</td>
<td>711</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>Engert et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lancet 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IIL</strong></td>
<td>6-8 x ABVD</td>
<td>61</td>
<td>168</td>
<td>73</td>
<td>84</td>
</tr>
<tr>
<td>Viviani et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEJM 2011</td>
<td></td>
<td></td>
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</tbody>
</table>

BEACOPP is obviously highly active with a very high progression free and overall survival rate.
ABVD: PET guided escalation strategy

**RATHL Trial**

- PET-CT 1 (Staging)
  - ABVD x 2
- PET-CT 2
  - PET -
    - AVD x 4
    - ABVD x 4
  - PET +
    - esc-BEACOPP x 3
- PET-CT 3
  - esc-BEACOPP x 1
  - XRT or salvage

Assess response
- Follow-up

**Study design**

**FIL-HD0801**

- IPS 0-7

**Stage IIB-IV**

2 ABVD

- PET
  - +
    - 4 ABVD
    - Salvage
  - -
    - PET
      - +
        - Random
        - RT bulky
      - -
        - No RT

- Phase II

**HD0607**

- GITIL

**IIB-IV; IPS 0-7**

- CT/PET

BEACOPP-esc. x 4

- R-BEACOPP-esc. x 4

- CT/PET

BEACOPP-bas. x 4

R-BEACOPP-bas. x 4

ASCT

- RT

No RT

Follow up
S0816: Progression-Free Survival (HIV-negative)

Median FU = 16.1 months

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Failed</th>
<th>2-Year Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>344</td>
<td>56</td>
<td>76% (95% CI: 69%, 81%)</td>
</tr>
</tbody>
</table>
Key objectives: safety, MTD, antitumor activity

Patients: 51 previously untreated HL patients (median age 33 years [range, 18–59]); disease stage: IIA bulky, n=3; IIB, n=8; IIIA, n=8; IIIB, n=9; IV, n=23; bulky disease, n=17; IPS ≥4, n=13

Treatment: Up to six 28-day cycles

- Brentuximab vedotin 0.6 (n=6), 0.9 (n=13), or 1.2 (n=6) mg/kg, days 1 and 15 (weeks 1 and 3), plus ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)
- Brentuximab vedotin 1.2 mg/kg (n=26) plus AVD (without bleomycin)
Safety: pulmonary toxicity

- Events generally occurred during Cycles 3-4
- Two patient deaths were associated with pulmonary toxicity
- Events resolved in 9 of 11 patients (82%)
  - Median time to resolution was 2.6 weeks (range, 1.6–5 weeks)
- 8 of 11 patients with events discontinued bleomycin and were able to complete treatment with AVD combined with brentuximab vedotin
- Concomitant administration of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity

Ansell SM, et al. ASH 2012, Atlanta, GA, USA (Abstract 798)
Peripheral neuropathy

<table>
<thead>
<tr>
<th>Preferred term*</th>
<th>ABVD with brentuximab vedotin N=25</th>
<th>AVD with brentuximab vedotin N=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>18 (72)</td>
<td>20 (77)</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>18 (72)</td>
<td>19 (73)</td>
</tr>
<tr>
<td>Peripheral motor neuropathy</td>
<td>3 (12)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>1 (4)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>1 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Summary of events using a standard MedDRA query (SMQ), regardless of relationship or severity

- Events were managed with dose modifications
- Most events were Grade 1 or 2 and no events were Grade 4 or 5
- One patient experienced Grade 3 events of peripheral sensory neuropathy (fingers and toes) and peripheral motor neuropathy (hands and feet)
- Overall, 6 of 51 patients discontinued brentuximab vedotin due to peripheral neuropathy; these discontinuations occurred in Cycles 5 or 6

Ansell SM, et al. ASH 2012, Atlanta, GA, USA (Abstract 798)
Anti-tumour activity

- **DLT:** No protocol-defined DLTs observed with either ABVD or AVD in combination with brentuximab vedotin (up to the maximum planned dose of 1.2 mg/kg)

- **Antitumor activity:**

<table>
<thead>
<tr>
<th>Response at end of frontline therapy, n (%)*</th>
<th>ABVD with brentuximab vedotin (n=22)</th>
<th>AVD with brentuximab vedotin (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>21 (95)</td>
<td>24 (96)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Not evaluable due to AE</td>
<td>1 (5)**</td>
<td>0</td>
</tr>
</tbody>
</table>

- Prior to completion of frontline therapy
  - 1 patient withdrew consent
  - 3 patients lost to follow-up

- Phase 3 study ongoing to assess treatment with brentuximab vedotin in combination with AVD compared to ABVD alone in treatment-naive patients

* Per Investigator
** Patient had Grade 5 pulmonary toxicity prior to end of frontline therapy

Ansell SM, et al. ASH 2012, Atlanta, GA, USA (Abstract 798)
A-B)VD-A failure free survival

Connors et al., ASH, 2014, abs 624

A-AVD Ergebnisse

CR 96 %
3-y FFS 92 %
3-y OS 100 %
Phase III study of A-AVD versus ABVD in advanced stage HL (NCT01712490)

Worldwide recruiting industry sponsored trial
Primary endpoint PFS: Estimates in C25003 (ECHELON I)

PFS @ 3 years for stage III/IV patients

<table>
<thead>
<tr>
<th></th>
<th>6x ABVD C 25003</th>
<th>6x AVD-A C 25003</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>75 expected</td>
<td>82.5 expected</td>
</tr>
</tbody>
</table>
Targeted BEACOPP: Study flow

Randomisation
Patients aged 18-60
CS IIB + RF ED or LMM, CS III/IV

2 x BrECAPP 2 x BrECADD

Interim Staging (CT-2/PET-2)

4 x BrECAPP 4 x BrECADD

Off study in case of PD

Off study in case of PD

End of therapy AND residual nodes > 2.5 cm:
PET positiv: Rx @30 Gy
PET negative: Follow up
Can we define patients at risk for treatment related mortality (TRM)?

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
</tr>
<tr>
<td>≥50</td>
<td>2</td>
</tr>
<tr>
<td>ECOG /</td>
<td></td>
</tr>
<tr>
<td>Karnofsky</td>
<td></td>
</tr>
<tr>
<td>&lt;2 or ≥80</td>
<td>0</td>
</tr>
<tr>
<td>=2 or &lt;80</td>
<td>1</td>
</tr>
</tbody>
</table>

Wongso et al., JCO, 2013